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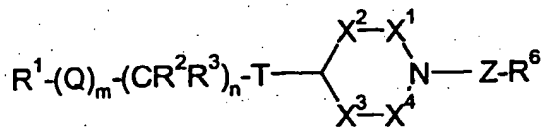
(54) Title: SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(I)

(57) Abstract: The invention provides compounds of formula (I) wherein R^1, R^2, R^3, R^6, Z, Q, m, n, X^1, X^2, X^3, X^4 and T are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them, and their use in therapy, especially for the treatment of chemokine receptor related diseases and conditions.

SUBSTITUTED PIPERIDINE COMPOUNDS USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

The present invention relates to substituted piperidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

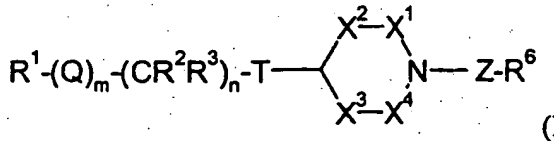
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention provides a compound of formula (I):



(I)

wherein

Z is CR^4R^5, C(O) or CR^4R^5-Z^1;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as CH=CH) or C(O)NH;

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy (such as methoxy or ethoxy), C_1-C_6 alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_1-C_6 alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl (such as CF_3), phenyl(C_1-C_6 alkyl) (such as benzyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents C_2-C_6 alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^7R^8$, $-C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or

more of halogen, oxo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3-C_7 cycloalkyl optionally substituted by C_1-C_4 alkyl;

T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$;

X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_1-C_4 alkyl or C_3-C_7 cycloalkyl(C_1-C_4 alkyl)} or C=O; or, when they are CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or phenyl(C_1-C_6 alkyl); and,

R^{15} and R^{20} are, independently, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or C_1-C_6 alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_1-C_6 alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is $C(O)NR^{10}$ and R^1 is optionally substituted phenyl then n is not 0.

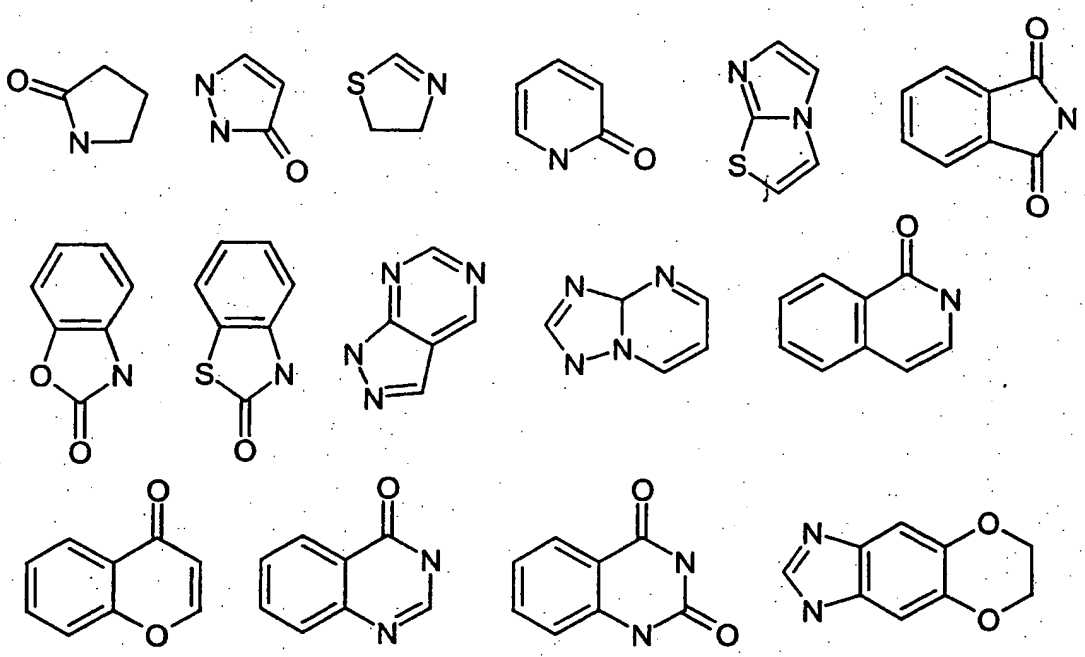
Certain compounds of formula (I) are capable of existing in isomeric forms (for example as tautomers, enantiomers, geometric isomers or diastereomers). The present invention encompasses all such isomers and mixtures thereof in all proportions.

Hydroxyalkyl is, for example, 2-hydroxyeth-1-yl. Haloalkyl is, for example, CF_3. Alkoxy is, for example, methoxy or ethoxy. Alkoxy(C_1-C_6 alkyl) is, for example, methoxymethyl or ethoxyethyl. Cycloalkyl is, for example, cyclopropyl or cyclohexyl. Cycloalkyl(C_1-C_6 alkyl) is, for example, cyclopropylmethyl. Alkylthio is, for example, methylthio or ethylthio. Alkylthio(C_1-C_6 alkyl) is, for example, methylthiomethyl. Alkylcarbonyloxy(C_1-C_6 alkyl) is, for example, $CH_3C(O)OCH_2$. $S(O)_2$(alkyl) is, for example, $CH_3S(O)_2$. Alkyl$S(O)_2$(C_1-C_6 alkyl) is, for example, $CH_3S(O)_2CH_2$. Aryl(C_1-C_6 alkyl) is, for example, benzyl, 2-phenyleth-1-yl or 1-phenyleth-1-yl. Heterocyclyl(C_1-C_6 alkyl) is, for example, heterocyclylmethyl. Aryl$S(O)_2$(C_1-C_6 alkyl) is, for example, phenyl$S(O)_2CH_2$. Heterocyclyl$S(O)_2$(C_1-C_6 alkyl) is, for example, heterocyclyl$S(O)_2CH_2$. Aryl(C_1-C_6 alkyl)$S(O)_2$ is, for example, benzyl$S(O)_2$. Heterocyclyl(C_1-C_6 alkyl)$S(O)_2$ is, for example, heterocyclyl$CH_2S(O)_2$. Alkenyl is, for example, vinyl or allyl. Carboxy-substituted C_1-C_6 alkoxy is, for example, $HOC(O)CH_2CH_2O$. Haloalkoxy is, for example, OCF_3. Hydroxyalkoxy is, for example, $HOCH_2CH_2O$. Alkylcarboxy-substituted C_1-C_6 alkoxy is, for example, $CH_3OC(O)CH_2CH_2O$. Aryloxy is, for example, phenoxy.

Heterocyclyloxy is, for example, pyridinyloxy or pyrimidinyloxy. C_3-C_7 cycloalkyl(C_1-C_6 alkylthio) is, for example, cyclopropylCH_2S. Alkynylthio is, for example, propargylthio. Alkylcarbonylamino is, for example, acylamino. Haloalkylcarbonylamino is, for example, $ClCH_2C(O)NH$. Alkoxycarbonyl is, for example, $CH_3OC(O)$.

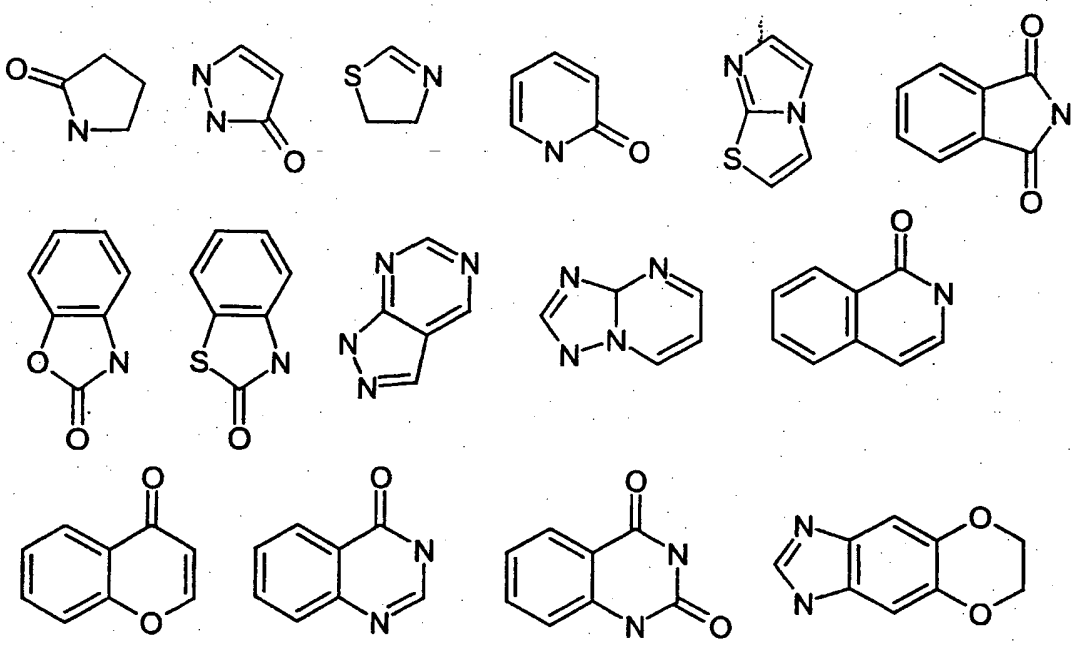
Aryl is a carbocyclic aromatic ring optionally fused to one or more carbocyclic rings. Aryl is, for example, phenyl, naphthyl or indanyl.

Heterocyclyl is an aromatic or non-aromatic ring system preferably comprising up to 6 (preferably up to 4) heteroatoms selected from the group comprising nitrogen, oxygen and sulphur, and preferably comprising one, two or three 5- or 6-membered rings. Heterocyclyl is, for example, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:

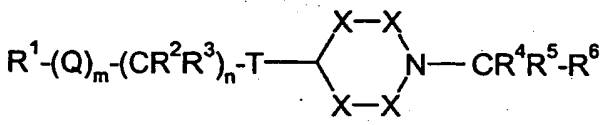


The group R^1 may represent an optionally substituted 3- to 14-membered (especially 5- to 10-membered) saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of R^1 ring systems, which can be moncyclic or polycyclic, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-

d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:



In one aspect the present invention provides a compound of formula (Ia):



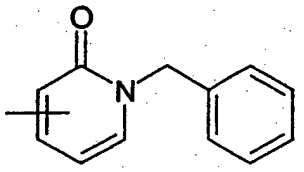
(Ia)

wherein

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio and C_1-C_6 alkoxycarbonyl, or

R^1 represents a 3- to 10-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, hydroxyl, carboxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylthiomethyl, C_1-C_6 alkylcarbonylamino, $-NR^7R^8$, $-C(O)NR^7R^8$, C_1-C_6

alkylcarbonyloxymethyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylpiperazinyl, furyl, phenyl, pyridinyl, pyrazinyl, halophenyl, thienyl, thienylmethyl, C_1-C_6 alkylbenzyl and



;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$ or $NR^9C(O)$;

n is 0, 1, 2, 3 or 4, provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group;

T represents a group NR^{10}, $C(O)NR^{10}$ or $NR^{11}C(O)NR^{10}$;

each X independently represents a group CH_2, CHR^{12} or C=O, provided that at least two groups X simultaneously represent CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 represents a phenyl group optionally substituted by one or more substituents independently selected from halogen, amino ($-NH_2$), nitro, cyano, sulphonyl ($-SO_3H$), sulphonamido ($-SO_2NH_2$), C_1-C_6 alkyl, C_1-C_6 haloalkoxy and C_1-C_6 alkylsulphonyl;

R^7 and R^8 each independently represent a hydrogen atom or a group selected from C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by phenyl; R^9, R^{10} and R^{11} each independently represent a hydrogen atom, or a C_1-C_4 alkyl or cyclopropylmethyl group; and

each R^{12} independently represents a C_1-C_4 alkyl or cyclopropylmethyl group;

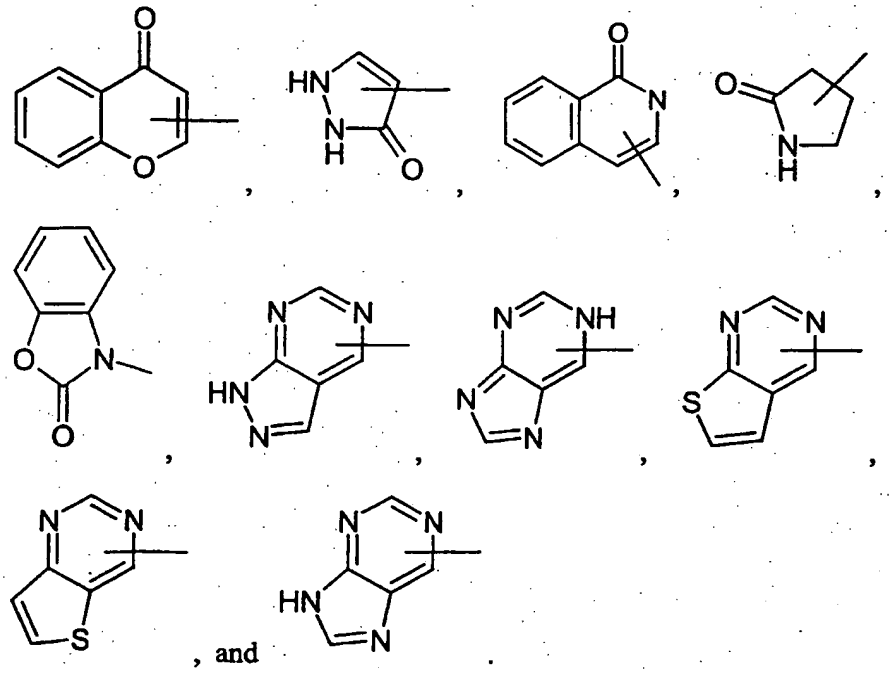
or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated an alkyl substituent or an alkyl moiety in a substituent group may be linear or branched. Examples of alkyl groups/moieties containing up to twelve carbon atoms include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl groups. A C_1-C_6 hydroxyalkyl group will comprise at least one hydroxyl group (e.g. one, two or three hydroxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. Similarly, a carboxy-substituted C_1-C_6 alkoxy group will comprise at least one carboxyl group (e.g. one, two or three

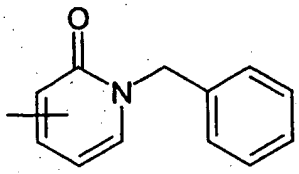
carboxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. A C_1-C_6 haloalkyl or C_1-C_6 haloalkoxy group will comprise at least one halogen atom (e.g. one, two, three or four halogen atoms independently selected from fluorine, chlorine, bromine and iodine) which may be attached to an internal or terminal carbon atom of the alkyl chain. A halophenyl group will comprise from 1 to 5 halogen atoms independently selected from fluorine, chlorine, bromine and iodine. A C_1-C_6 alkylbenzyl group will comprise at least one C_1-C_6 alkyl group (e.g. one, two or three C_1-C_6 alkyl groups) attached to the phenyl ring of the benzyl moiety. If there is more than one C_1-C_6 alkyl group attached to the phenyl ring, the groups may be the same or different. In a C_1-C_6 alkoxycarbonylpiperazinyl substituent group, the piperazinyl moiety is attached through a nitrogen atom to the carbonyl moiety. When T represents $C(O)NR^9$, it should be understood that the nitrogen atom is attached directly to the six-membered heterocyclic ring in formula (I).

The group R^1 may represent a C_1-C_{12}, preferably C_1-C_{10}, more preferably C_1-C_6, alkyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, alkylthio and C_1-C_6 alkoxycarbonyl, preferably C_1-C_4 alkoxycarbonyl.

The group R^1 may alternatively represent an optionally substituted 3- to 10-membered saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used which can be moncyclic or polycyclic include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyrazolyl, furyl, thienyl, imidazolyl, quinolinyl (e.g. 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), pyridinyl (e.g. 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), 1,3-benzodioxolyl, thiazolyl, benzimidazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl), triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), benzothiazolyl, pyrimidinyl (e.g. 2-pyrimidinyl or 4-pyrimidinyl), benzothienyl,



In a further aspect of the invention the ring system of R^1 may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine); cyano; nitro; hydroxyl; carboxyl; C_1-C_6, preferably C_1-C_4, alkyl (especially methyl or ethyl); C_1-C_6, preferably C_1-C_4, hydroxyalkyl; C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl); C_1-C_6, preferably C_1-C_4, alkoxy (especially methoxy, ethoxy, n-propoxy or isopropoxy); carboxy-substituted C_1-C_6, preferably C_1-C_4, alkoxy; C_1-C_6, preferably C_1-C_4, alkylthio (especially methylthio, ethylthio, n-propylthio and tert-butylthio); C_1-C_6, preferably C_1-C_4, alkylthiomethyl (particularly methylthiomethyl); C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (especially methylcarbonylamino); $-NR^7R^8$; $-C(O)NR^7R^8$; C_1-C_6, preferably C_1-C_4, alkylcarbonyloxymethyl (particularly methylcarbonyloxymethyl); C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (especially methoxycarbonyl or ethoxycarbonyl); C_1-C_6, preferably C_1-C_4, alkoxycarbonylpiperazinyl; furyl; phenyl; pyridinyl; pyrazinyl; halophenyl (especially chlorophenyl); thienyl; thienylmethyl; C_1-C_6, preferably C_1-C_4, alkylbenzyl (particularly methylbenzyl); and



In a further aspect R^1 is an aromatic 5-membered heterocyclyl having 2, 3 or 4 ring nitrogen atoms (for example 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole or tetrazole) substituted by one heteroaromatic ring (such as pyridine or pyrazole) which is itself optionally substituted by halogen or C_1-C_4 alkyl; or R^1 is halophenyl (for example phenyl optionally substituted (such as in the 4-position) by fluoro or chloro; such as 4-chlorophenyl or 4-fluorophenyl).

In a further aspect of the invention Q is oxygen or m is 0. In another aspect of the invention Q represents a sulphur atom or a group NH, C(O) or NHC(O).

In yet another aspect of the invention n is 1 or 2.

In a further aspect of the invention T represents a group NH, C(O)NH or NHC(O)NH. In another aspect of the invention T represents a NH or C(O)NH group. In a further aspect T is C(O)NH.

In one aspect X^1, X^2, X^3 and X^4 are all CH_2 or CHR^{12}, wherein the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form CH_2CH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2. In a still further aspect X^1, X^2, X^3 and X^4 are all CH_2. Preferably, all four groups X represent CH_2.

It is preferred that each R^2 and R^3 independently represents a hydrogen atom or a methyl group, especially a hydrogen atom.

In one aspect R^4 and R^5 are hydrogen or C_1-C_4 alkyl. In another aspect R^4 and R^5 preferably each represent a hydrogen atom.

In another aspect of the invention R^6 represents a phenyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, haloalkoxy, methylenedioxy and C_1-C_6, preferably C_1-C_4, alkylsulphonyl.

In another aspect of the invention R^6 represents a phenyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, haloalkoxy and C_1-C_6, preferably C_1-C_4, alkylsulphonyl.

In a further aspect R^6 is phenyl optionally substituted by halogen or methylenedioxy. In a still further aspect R^6 is most preferably a phenyl group substituted by halogen. Examples of R^6 include 3-chlorophenyl, 4-chlorophenyl or, especially, 3,4-dichlorophenyl.

R^7 and R^8 each independently represent a hydrogen atom or a group selected from C_1-C_6, preferably C_1-C_4, hydroxyalkyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) and C_1-C_6, preferably C_1-C_4, alkyl optionally substituted by phenyl (e.g. one or two phenyl groups).

Most preferably, R^7 and R^8 each independently represent a hydrogen atom, or a group selected from C_2 hydroxyalkyl, cyclopropyl and C_1-C_2 alkyl optionally substituted by phenyl.

Compounds of the invention include all the Examples below, some of which are:
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine,
N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide,
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol,
N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine,
N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine,
N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol,
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one,
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine,
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine,
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate,
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,
N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid,
N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid,
N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid,
N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine,
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine,
Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide,
2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide,
3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide,
2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide,

2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide,

5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-phenylethyl)phthalamide,

2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide,

2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide,

tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine,

2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol,

N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine,

N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^2,6-dimethyl-2,4-pyrimidinediamine,

2-Chloro-N^4-cyclopropyl-N^6-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine,

N^2-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^4,6-dimethyl-2,4-pyrimidinediamine,

N^4-Cyclopropyl-N^2-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1H-purin-6-yl)-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine,

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide,

2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine,

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt,

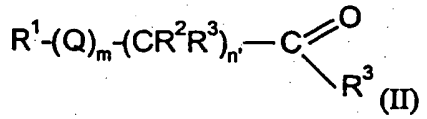
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea, and

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt.

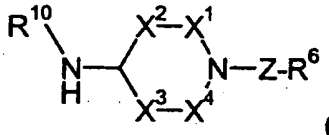
The present invention further provides a process for the preparation of a compound of formula (I) or (Ia) which comprises:

(a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10}, reacting a compound of formula



(II)

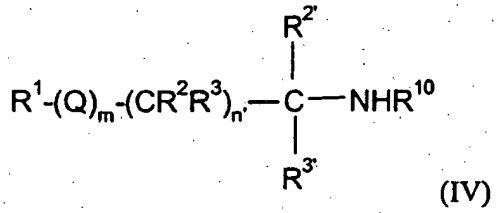
wherein n' is 0 or an integer from 1 to 3 and R^1, R^2, R^3, m and Q are as defined above, with a compound of formula



(III)

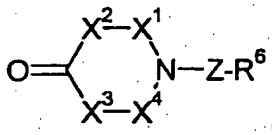
or a salt thereof, wherein X^1, X^2, X^3, X^4, Z, R^6 and R^{10} are as defined above, in the presence of a reducing agent; or

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1\text{-}C_4 \text{ alkyl})_2$ and T is NR^{10}, reacting a compound of formula



(IV)

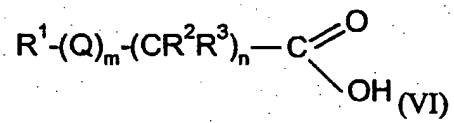
wherein n' is 0 or an integer from 1 to 3, $R^{2'}$ and $R^{3'}$ each independently represent a $C_1\text{-}C_4$ alkyl group, and R^1, R^2, R^3, R^{10}, m and Q are as defined above, with a compound of formula



(V)

wherein X^1, X^2, X^3, X^4, Z and R^6 are as defined above, in the presence of a reducing agent; or

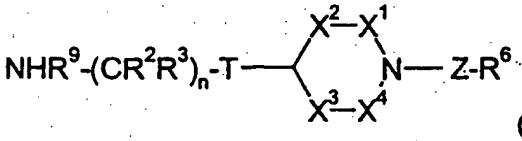
(c) when T is $C(O)NR^{10}$, reacting a compound of formula



(VI)

wherein R^1, R^2, R^3, Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

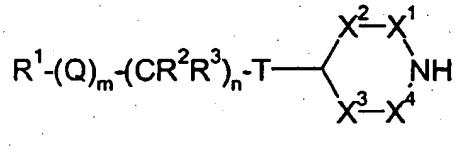
(d) when m is 1 and Q is NR^9, reacting a compound of formula (VII), R^1 - L^1, wherein L^1 represents a leaving group (e.g. a halogen atom) and R^1 is as defined above, with a compound of formula



(VIII)

or a salt thereof, wherein n, T, X^1, X^2, X^3, X^4, Z, R^2, R^3, R^6 and R^9 are as defined above; or

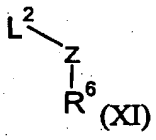
(e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of formula



(IX)

or a salt thereof, wherein R^1, R^2, R^3, Q, m, n, X^1, X^2, X^3, X^4 and T are as defined above, with a compound of general formula (X), R^6 - C(O) - R^{20}, wherein R^{20} represents a hydrogen atom or a C_1-C_4 alkyl group and R^6 is as defined above, in the presence of a reducing agent; or

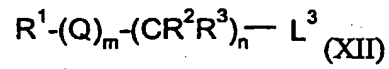
(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of formula



(XI)

wherein L^2 represents a leaving group (e.g. a halogen atom) and Z and R^6 are as defined above; or

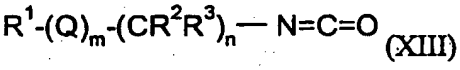
(g) when T is NR^{10}, reacting a compound of formula



(XII)

wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1, R^2, R^3, m, n and Q are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

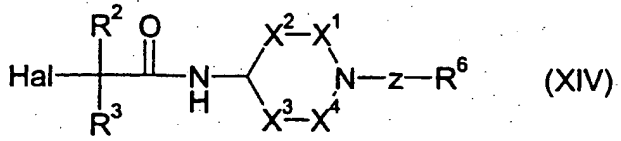
(h) when T is $NHC(O)NR^{10}$, reacting a compound of formula



(XIII)

wherein R^1, R^2, R^3, Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above; or

(i) when T is C(O)NH, Z is CH_2, n is 1, R^2 and R^3 are hydrogen or C_1-C_4 alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV):



(XIV)

wherein Hal is a suitable halogen (such as bromo or chloro), R^2, R^3, X^1, X^2, X^3, X^4, Z and R^6 are as defined above, with R^1OH or R^1SH in the presence of a suitable base (such as potassium carbonate or sodium or potassium hydroxide);

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) or (Ia)obtained.

Compounds of formulae (II) to (XIV) are either commercially available, or are known in the literature or may be prepared using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) or (Ia) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

The compounds of formula (I) and (Ia) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity. More particularly, the compounds have utility as modulators of the activity of chemokine receptors CCR1 and/or CCR3.

A further aspect of the invention involves the use of a compound of formula (I) or (Ia) in the treatment of conditions or diseases in which modulation of chemokine receptor activity is beneficial.

Thus, compounds of formula (I) or (Ia) may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS). Examples of these conditions include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; and

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

Thus, the present invention provides a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In another aspect the present invention provides the use of a compound of formula (I), wherein Z is CR^4R^5, C(O) or CR^4R^5-Z^1; Z^1 is C_{1-4} alkylene, C_{2-4} alkenylene or C(O)NH; R^1

represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_{3-7} cycloalkyl, C_1-C_6 alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2(C_1$-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or R^1 represents C_2-C_6 alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2(C_1$-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2(C_1$-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2(C_1$-C_6 alkyl), heterocyclyl$S(O)_2(C_1$-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^7R^8$, $-C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2(C_1$-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl; m is 0 or 1; Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH; n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0; each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3-C_7 cycloalkyl optionally substituted by C_1-C_4 alkyl; T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$; X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_1-C_4 alkyl or C_3-C_7 cycloalkyl(C_1-C_4 alkyl)} or C=O; or, when they are

CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2; R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group; R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkylS(O)$_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), arylS(O)$_2$(C_1-C_6 alkyl), heterocyclylS(O)$_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)S(O)$_2$, heterocyclyl(C_1-C_6 alkyl)S(O)$_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, S(O)$_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl; R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or phenyl(C_1-C_6 alkyl); R^{15} and R^{20} are, independently, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or C_1-C_6 alkyl optionally substituted by phenyl; and, R^{25} and R^{26} are, independently, C_1-C_6 alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, S(O)$_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; in the manufacture of a medicament for the modulation of a chemokine receptor (such as CCR1 or CCR3). In a further aspect such medicament is for the treatment of asthma.

The invention also provides a method of treating an inflammatory disease in a person suffering from, or at risk of, said disease, which comprises administering to the person a therapeutically effective amount of a compound of formula (I) or (Ia), or a

pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

A compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate or solvate of a salt, may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) or (Ia) compound, salt, solvate or solvate of salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

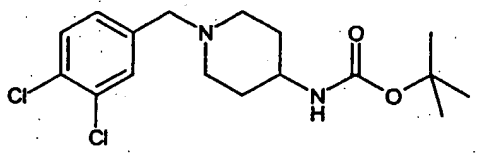
The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders, aerosols or granules, or by parenteral administration in

the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will be further explained by reference to the following illustrative examples.

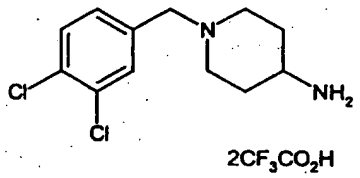
Examples 1-47

(i) tert-Butyl 1-(3,4-dichlorobenzyl)-4-piperidinylcarbamate



Sodium triacetoxyborohydride (6g) was added to a stirred solution of 3,4-dichlorobenzaldehyde (4.2g) and 1,1-dimethylethyl-4-piperidinyl carbamate (4g) in dichloromethane (50ml). The mixture was stirred at room temperature for 4h then partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether to give a white solid (3.5g). Used directly.

(ii) 1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt



The product from step (i) (3.5g) was treated with trifluoroacetic acid (10ml) in dichloromethane (40ml). After 72h, the solution was evaporated, the residue triturated with ether and the solid (4.3g) collected.

MS: APCI(+ve) 259/61 (M+1)

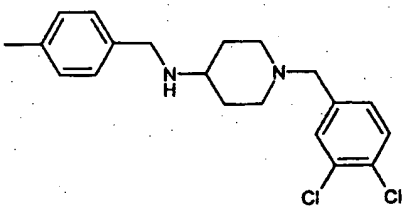
(iii) Examples 1-47

The product from step (ii) (2mg), the appropriate aldehyde (2 equivalents), sodium triacetoxyborohydride (3 equivalents) and diisopropylethylamine (2 equivalents) in

acetonitrile (0.08ml) and 1-methyl-2-pyrrolidinone (0.12ml) was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

Example 1

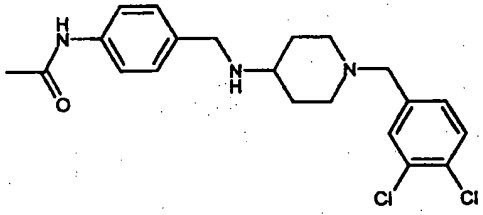
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine



MS: APCI(+ve) 363 (M+1)

Example 2

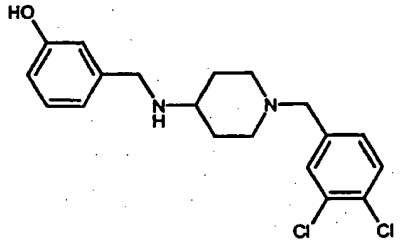
N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide



MS: APCI(+ve) 406 (M+1)

Example 3

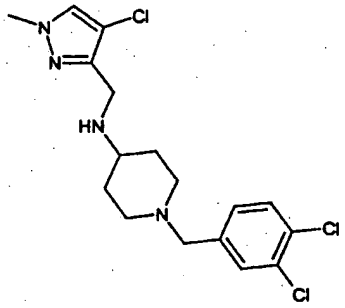
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol



MS: APCI(+ve) 365 (M+1)

Example 4

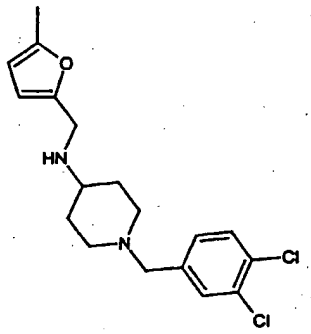
N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 389 (M+1)

Example 5

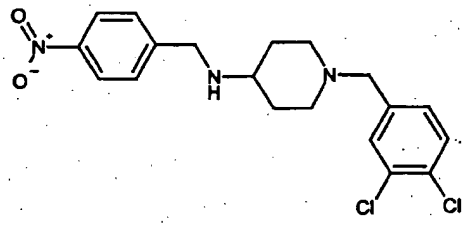
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine



MS: APCI(+ve) 353 (M+1)

Example 6

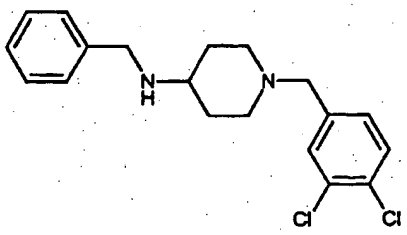
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine



MS: APCI(+ve) 394 (M+1)

Example 7

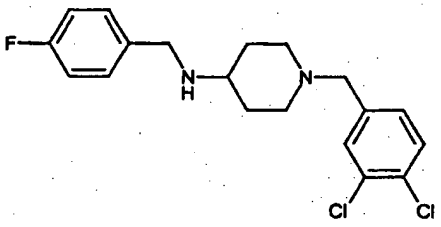
N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 349 (M+1)

Example 8

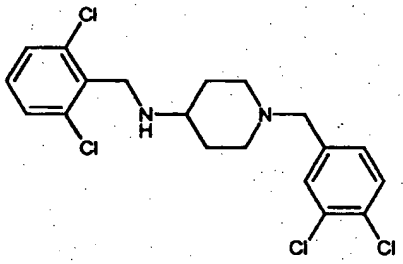
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine



MS: APCI(+ve) 367 (M+1)

Example 9

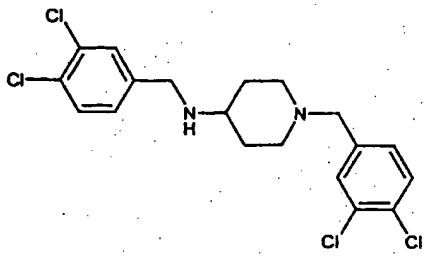
N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 10

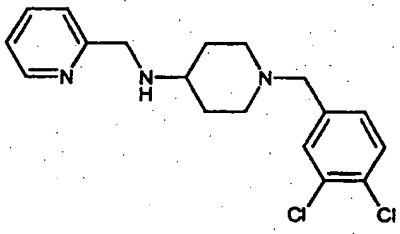
N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 11

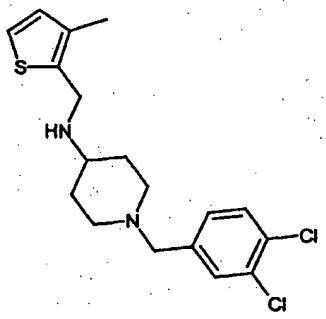
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 12

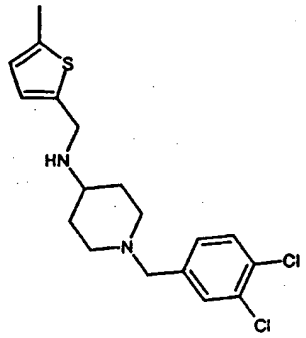
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine



MS: APCI(+ve) 369 (M+1)

Example 13

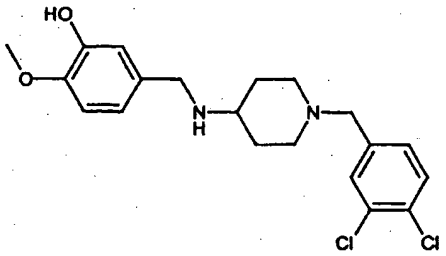
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine



MS: APCI(+ve) 369 (M+1)

Example 14

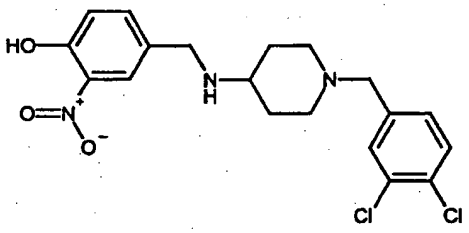
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol



MS: APCI(+ve) 395 (M+1)

Example 15

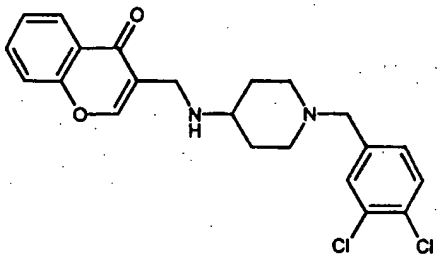
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



MS: APCI(+ve) 410 (M+1)

Example 16

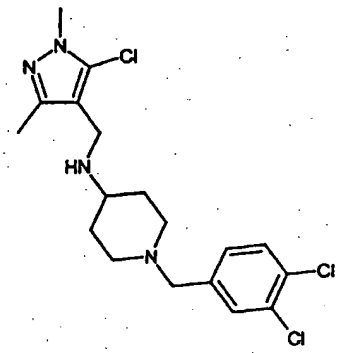
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one



MS: APCI(+ve) 417 (M+1)

Example 17

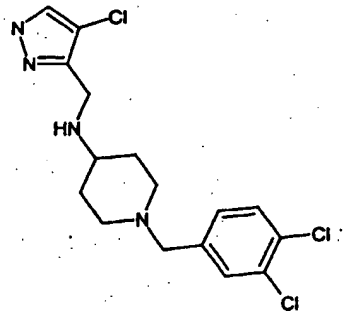
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 403 (M+1)

Example 18

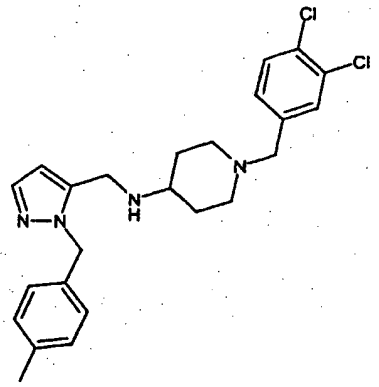
N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 373 (M+1)

Example 19

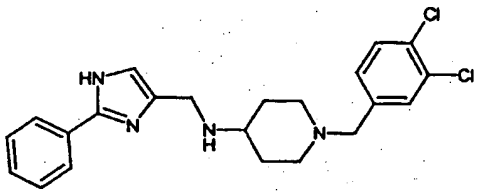
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine



MS: APCI(+ve) 443 (M+1)

Example 20

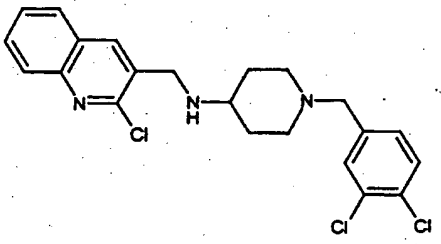
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine



MS: APCI(+ve) 414 (M+1)

Example 21

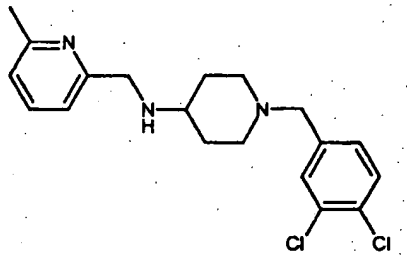
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 434 (M+1)

Example 22

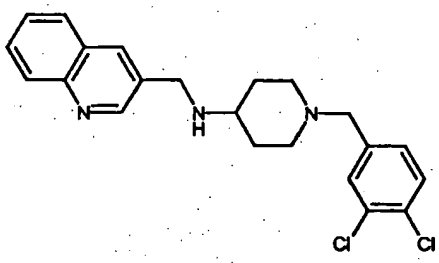
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine



MS: APCI(+ve) 364 (M+1)

Example 23

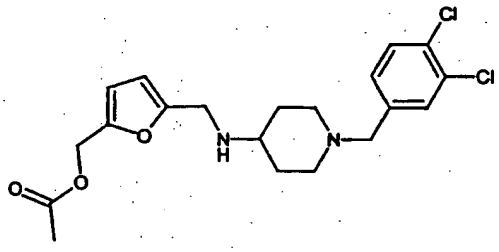
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 24

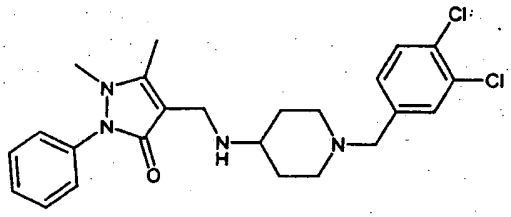
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate



MS: APCI(+ve) 411 (M+1)

Example 25

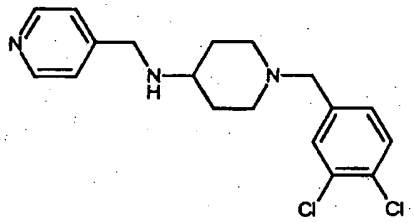
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one



MS: APCI(+ve) 459 (M+1)

Example 26

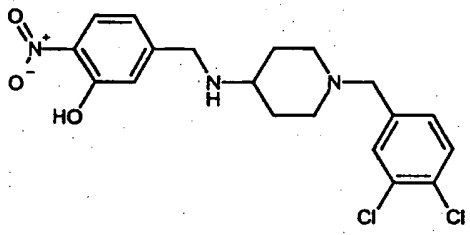
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 27

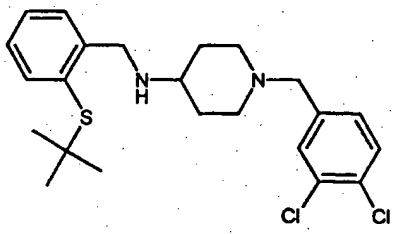
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



MS: APCI(+ve) 410 (M+1)

Example 28

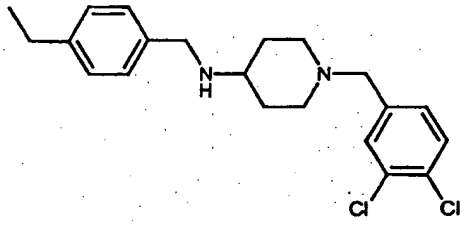
N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 437 (M+1)

Example 29

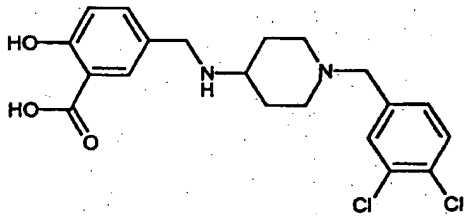
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine



MS: APCI(+ve) 377 (M+1)

Example 30

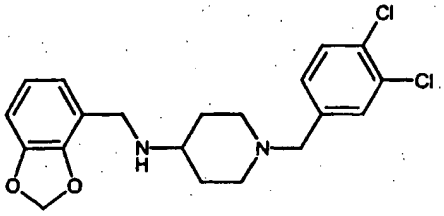
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid



MS: APCI(+ve) 409 (M+1)

Example 31

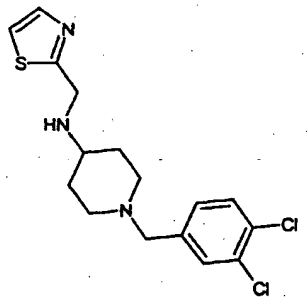
N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 393 (M+1)

Example 32

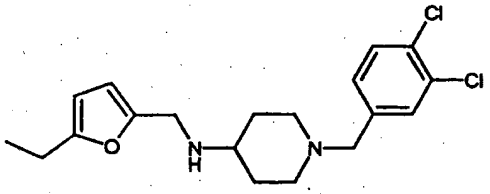
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine



MS: APCI(+ve) 356 (M+1)

Example 33

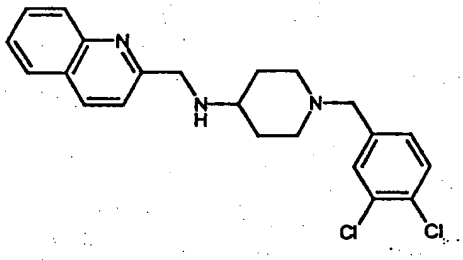
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine



MS: APCI(+ve) 367 (M+1)

Example 34

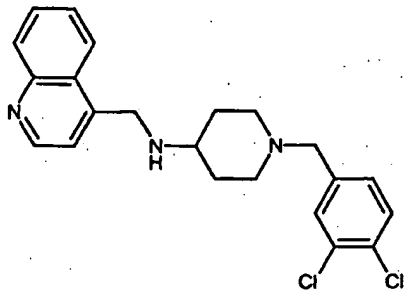
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 35

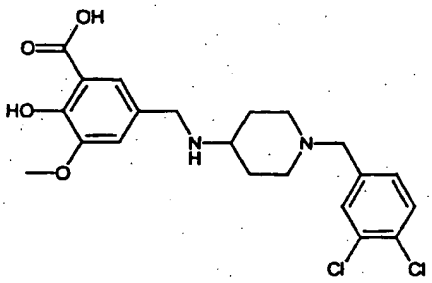
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 36

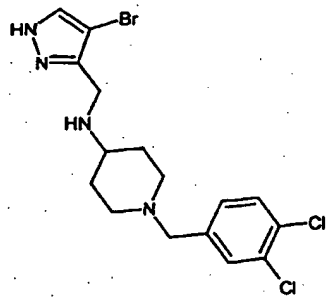
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid



MS: APCI(+ve) 439 (M+1)

Example 37

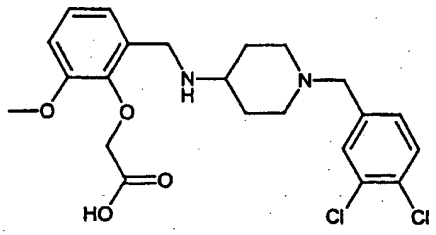
N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 38

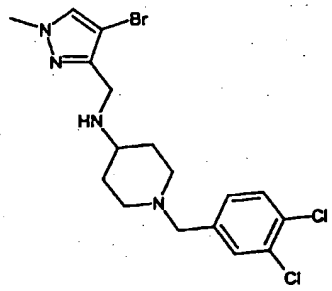
2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid



MS: APCI(+ve) 453 (M+1)

Example 39

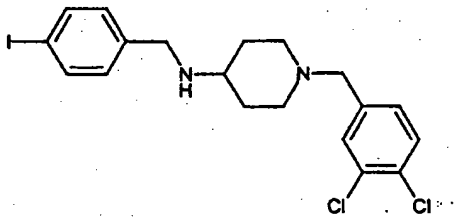
N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 433 (M+1)

Example 40

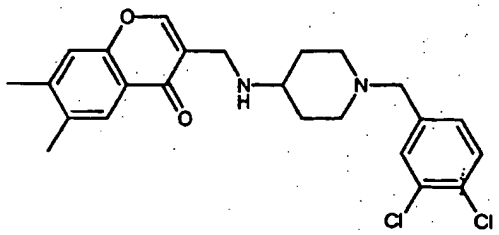
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine



MS: APCI(+ve) 475 (M+1)

Example 41

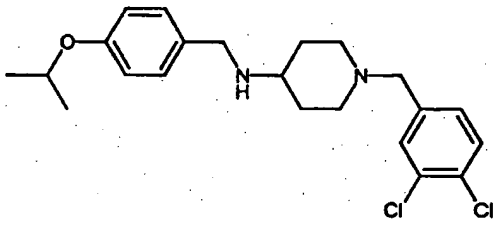
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one



MS: APCI(+ve) 445 (M+1)

Example 42

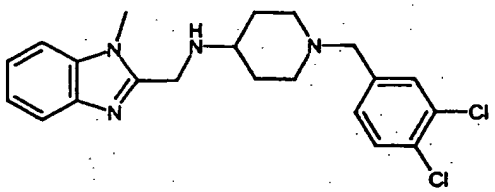
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine



MS: APCI(+ve) 407 (M+1)

Example 43

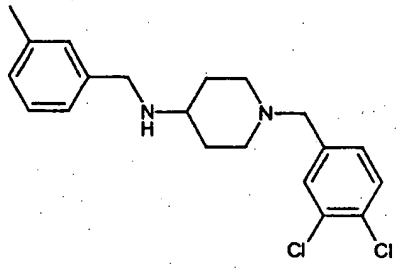
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine



MS: APCI(+ve) 403 (M+1)

Example 44

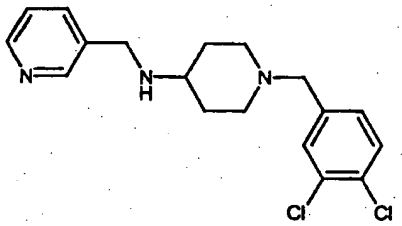
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine



MS: APCI(+ve) 363 (M+1)

Example 45

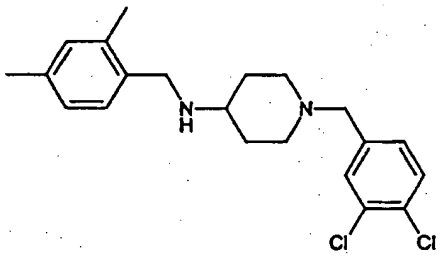
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 46

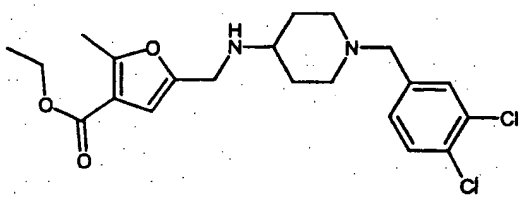
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine



MS: APCI(+ve) 377 (M+1)

Example 47

Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate



MS: APCI(+ve) 425 (M+1)

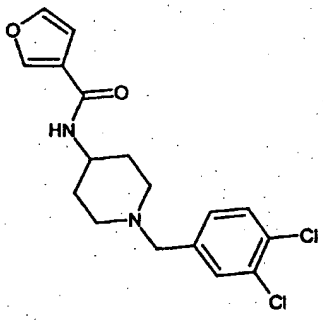
Examples 48-73

(i) Examples 48-73

Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (2 equiv) was added to a solution of the product from Example 1 step (ii) (hydrochloride salt) (1mg), the appropriate acid (2 equivalents) and diisopropylethylamine (5 equivalents) in dimethylformamide (0.17ml) and was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.3ml).

Example 48

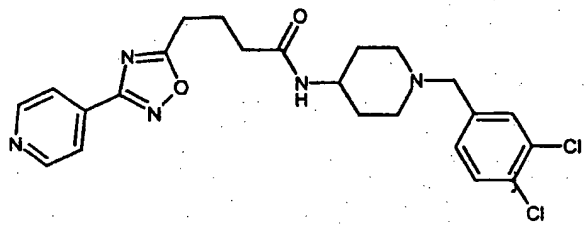
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide



MS: APCI(+ve) 353 (M+1)

Example 49

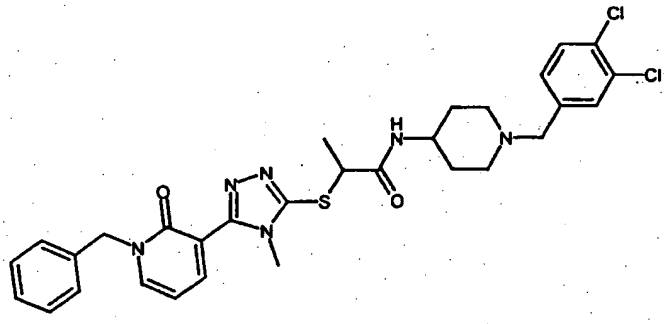
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide



MS: APCI(+ve) 474 (M+1)

Example 50

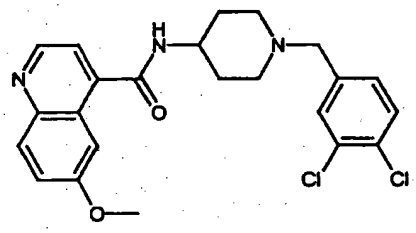
2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



MS: APCI(+ve) 611 (M+1)

Example 51

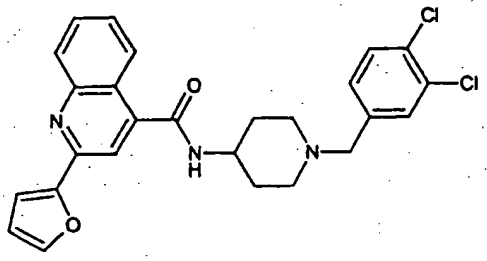
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide



MS: APCI(+ve) 444 (M+1)

Example 52

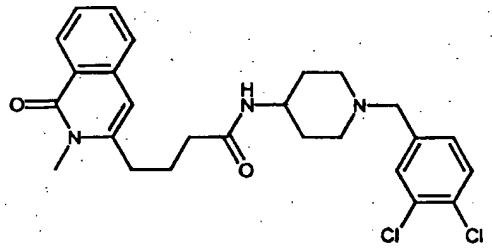
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide



MS: APCI(+ve) 480 (M+1)

Example 53

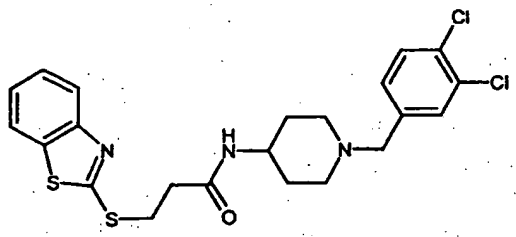
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide



MS: APCI(+ve) 486 (M+1)

Example 54

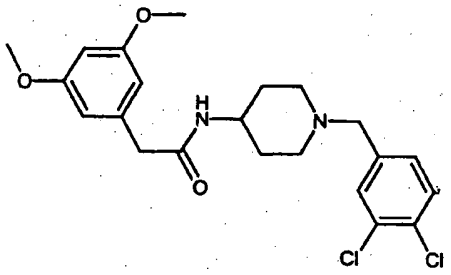
3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



MS: APCI(+ve) 480 (M+1)

Example 55

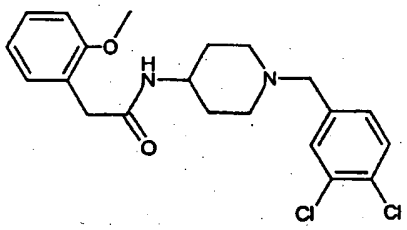
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide



MS: APCI(+ve) 437 (M+1)

Example 56

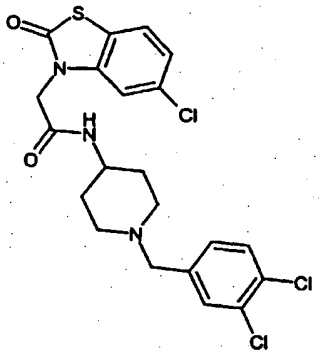
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide



MS: APCI(+ve) 407 (M+1)

Example 57

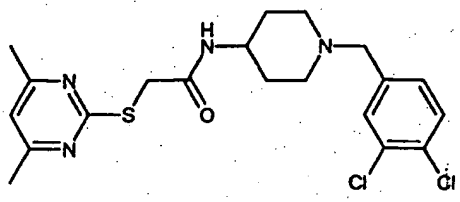
2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 486 (M+1)

Example 58

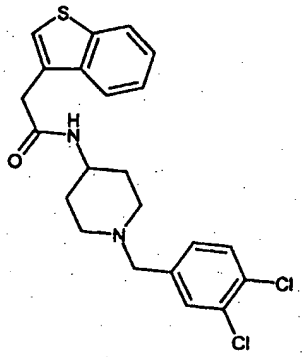
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide



MS: APCI(+ve) 439 (M+1)

Example 59

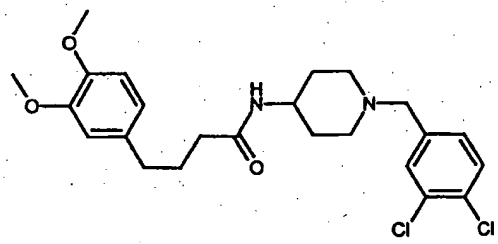
2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 433 (M+1)

Example 60

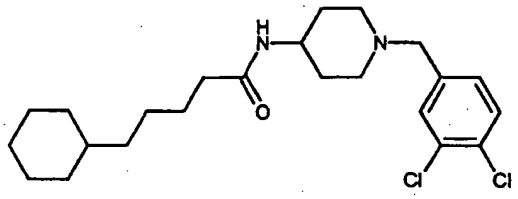
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide



MS: APCI(+ve) 465 (M+1)

Example 61

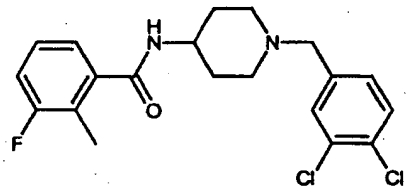
5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide



MS: APCI(+ve) 425 (M+1)

Example 62

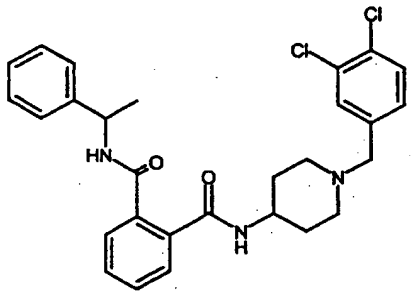
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide



MS: APCI(+ve) 395 (M+1)

Example 63

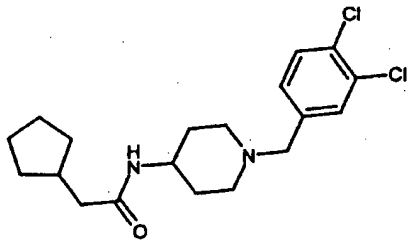
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-phenylethyl)phthalamide



MS: APCI(+ve) 510 (M+1)

Example 64

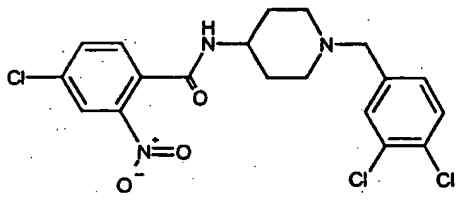
2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 369 (M+1)

Example 65

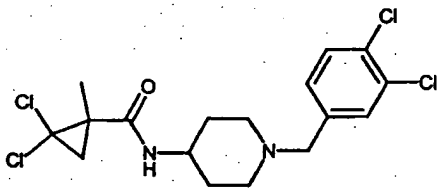
4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide



MS: APCI(+ve) 444 (M+1)

Example 66

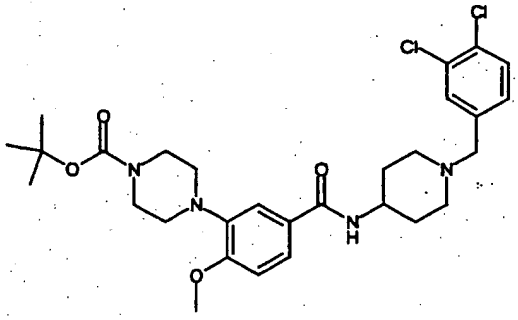
2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide



MS: APCI(+ve) 411 (M+1)

Example 67

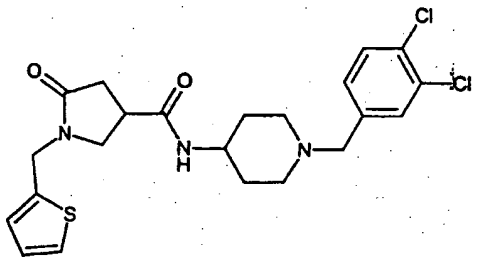
tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate



MS: APCI(+ve) 577 (M+1)

Example 68

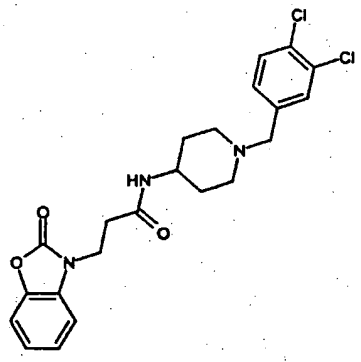
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide



MS: APCI(+ve) 466 (M+1)

Example 69

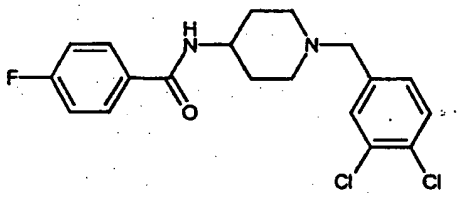
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide



MS: APCI(+ve) 448 (M+1)

Example 70

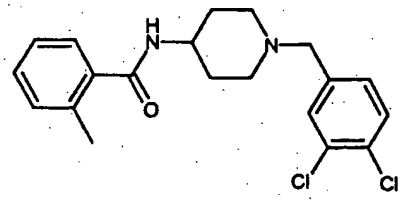
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide



MS: APCI(+ve) 381 (M+1)

Example 71

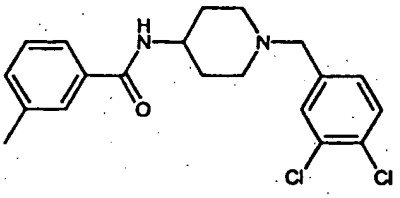
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide



MS: APCI(+ve) 377 (M+1)

Example 72

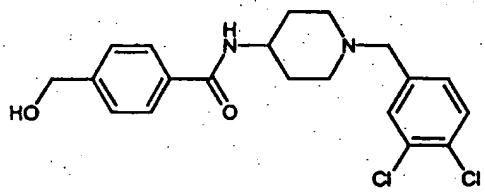
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide



MS: APCI(+ve) 377 (M+1)

Example 73

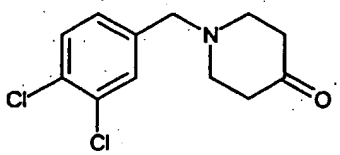
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide



MS: APCI(+ve) 393 (M+1)

Examples 74-93

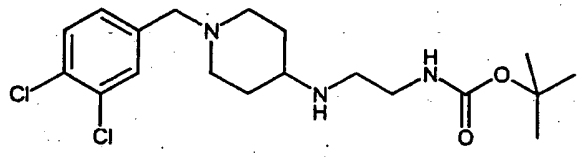
(i) 1-(3,4-Dichlorobenzyl)-4-piperidinone



A solution of 3,4-dichlorobenzyl chloride (2.8ml), 4-ketopiperidine hydrochloride monohydrate and triethylamine (8ml) in dimethylformamide (30ml) was stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate, the

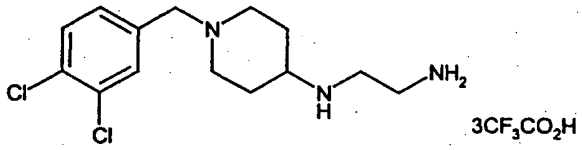
organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 40-50% ethyl acetate/isohexane. Yield 2.1g.
MS: APCI(+ve) 258/60 (M+1)

(ii) tert-Butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate



A solution of the product from step (i) (1.61g), N-(tert-butoxycarbonyl)-ethylenediamine (1g) and sodium triacetoxyborohydride (2.12g) in dichloromethane (20ml) was stirred at room temperature for 3h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Yield 1.28g.
MS: APCI(+ve) 402/4 (M+1)

(iii) N-1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine, tri-trifluoroacetate salt



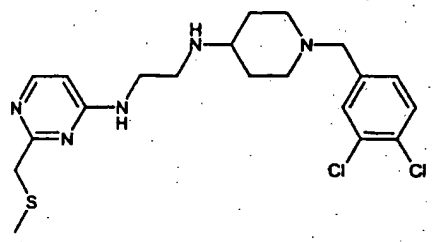
The product from step (ii) (1.28g) was treated with trifluoroacetic acid (5ml) in dichloromethane (10ml). After 20h, the solution was evaporated, the residue triturated with ether and the solid (1.62g) collected.
MS: APCI(+ve) 302/4 (M+1)

(iv) Examples 74-93

The product from step (iii) (0.0026g), the appropriate activated halo-aromatic (1.25 equivalents) and diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrolidinone (0.15ml) was heated at 100°C for 20h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

Example 74

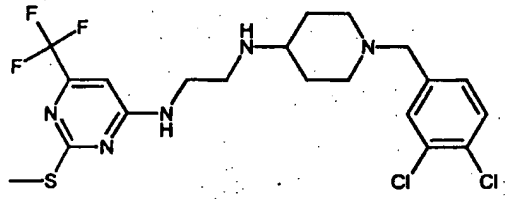
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine



MS: APCI(+ve) 440(M+1)

Example 75

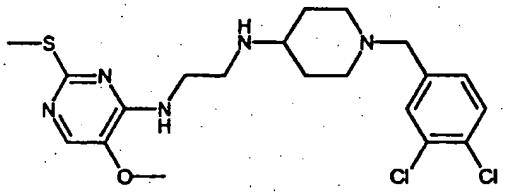
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 494(M+1)

Example 76

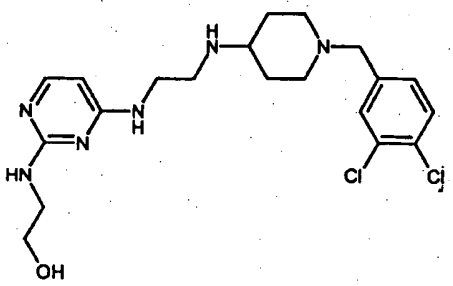
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 456(M+1)

Example 77

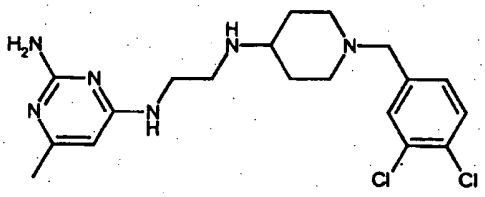
2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol



MS: APCI(+ve) 439(M+1)

Example 78

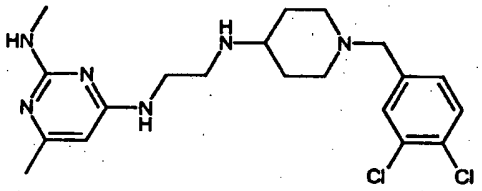
N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine



MS: APCI(+ve) 409(M+1)

Example 79

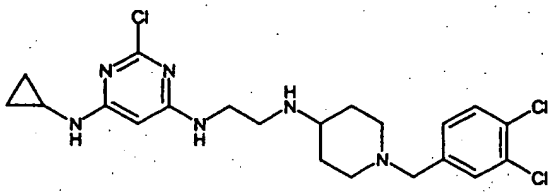
N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^2,6-dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 423(M+1)

Example 80

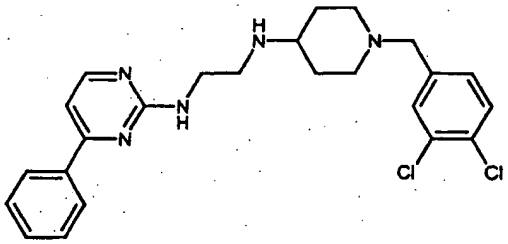
2-Chloro-N^4-cyclopropyl-N^6-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine



MS: APCI(+ve) 471(M+1)

Example 81

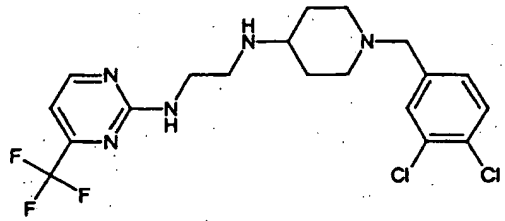
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine



MS: APCI(+ve) 456(M+1)

Example 82

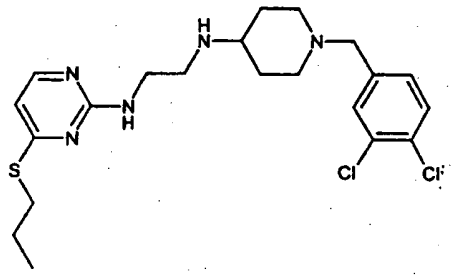
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 448(M+1)

Example 83

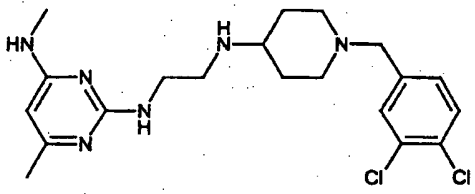
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 454(M+1)

Example 84

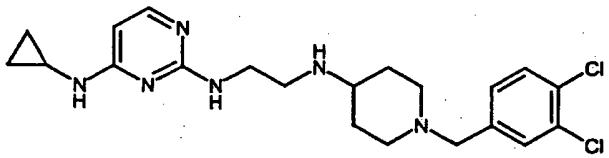
N^2-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^4,6-dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 423(M+1)

Example 85

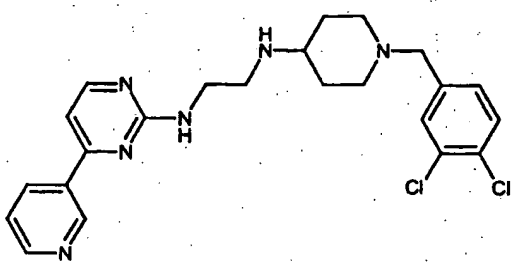
N^4-Cyclopropyl-N^2-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine



MS: APCI(+ve) 435(M+1)

Example 86

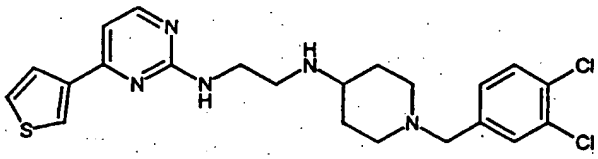
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 457(M+1)

Example 87

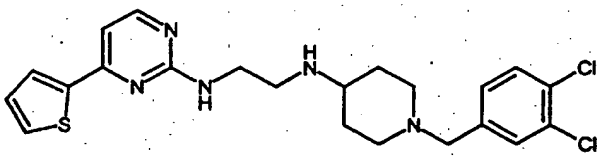
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 462(M+1)

Example 88

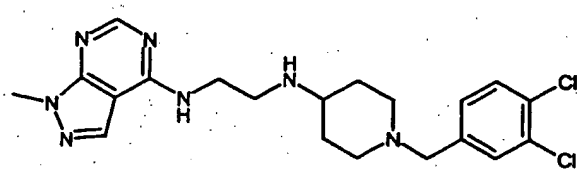
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 462(M+1)

Example 89

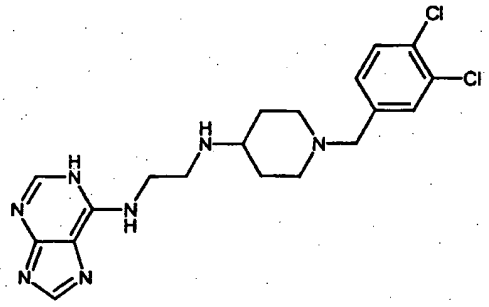
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 434(M+1)

Example 90

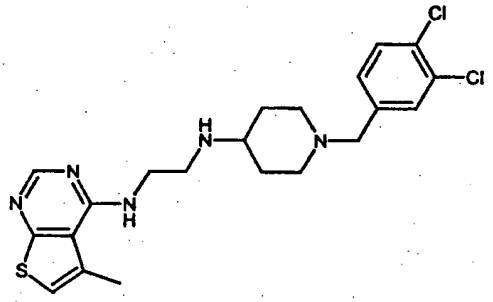
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1H-purin-6-yl)-1,2-ethanediamine



MS: APCI(+ve) 420(M+1)

Example 91

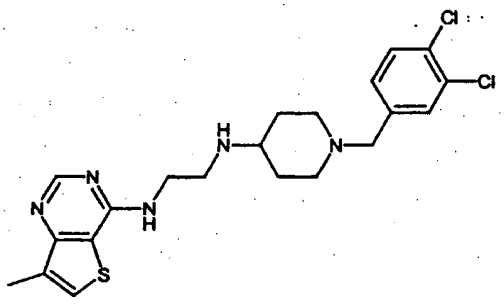
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 450(M+1)

Example 92

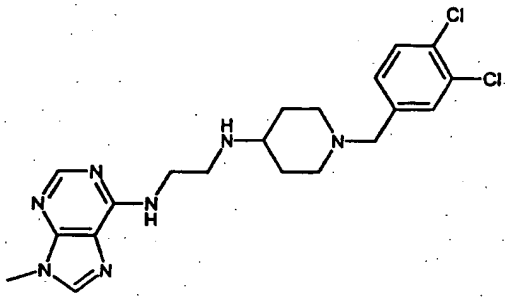
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 450(M+1)

Example 93

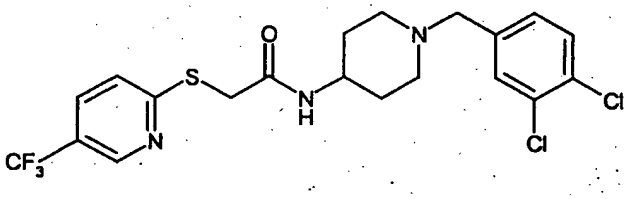
N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine



MS: APCI(+ve) 434(M+1)

Example 94

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide



Carbonyldiimidazole (0.105g) was added to a stirred solution of 2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetic acid (0.166g) in dimethylformamide (2ml). After 1h a solution of the product from Example 1 step (ii) (0.3g) in a solution of dimethylformamide and diisopropylethylamine (2 equivalents) (1.5ml) was added and stirred at room temperature for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether and collected. Yield 0.084g as a solid.

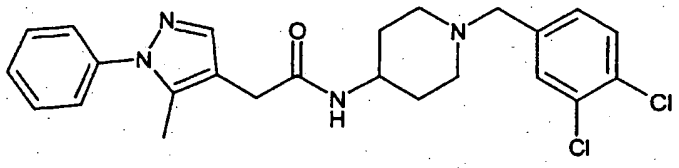
MS: APCI(+ve) 478/80 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.76(s, 1H), 8.11(d, 1H), 8.02(dd, 1H), 7.59-7.53(m, 3H), 7.29(dd, 1H), 3.91(s, 1H), 3.58-3.45(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.70(br d, 2H), 1.46-1.37(m, 2H).

MP: 98°C

Example 95

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.151g) using the method of Example 94. Yield 0.18g as a solid.

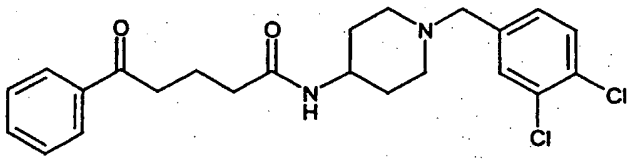
MS: APCI(+ve) 457/9 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.90(d, 1H), 7.59-7.38(m, 8H), 7.29(dd, 1H), 3.54-3.50(m, 1H), 3.45(s, 2H), 3.24(s, 2H), 2.72(br d, 2H), 2.24(s, 3H), 2.03(br t, 2H), 1.72(br d, 2H), 1.46-1.37(m, 2H).

MP: 165°C

Example 96

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 5-oxo-5-phenylpentanoic acid (0.134g) using the method of Example 94. Yield 0.149g as a solid.

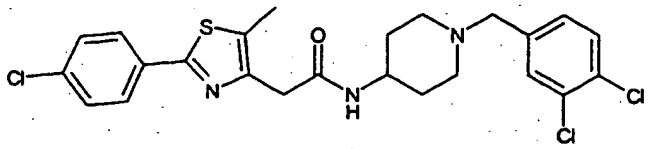
MS: APCI(+ve) 433/5 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.96-7.93(m, 2H), 7.72(d, 1H), 7.65-7.50(m, 5H), 7.28(dd, 1H), 3.57-3.48(m, 1H), 3.44(s, 2H), 3.01(t, 2H), 2.72-2.67(m, 2H), 2.13(t, 2H), 2.04-1.98(m, 2H), 1.86-1.79(m, 2H), 1.69(br s, 2H), 1.41-1.32(m, 2H).

MP: 130°C

Example 97

2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(4-chlorophenyl)-5-methyl-1,3-thiazol-4-yl]acetic acid (0.187g) using the method of Example 94. Yield 0.1g as a solid.

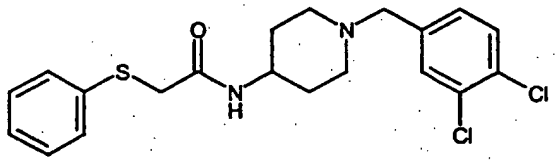
MS: APCI(+ve) 510/2 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.00(d, 1H), 7.85-7.82(m, 2H), 7.59-7.52(m, 4H), 7.29(dd, 1H), 3.57-3.51(m, 3H), 3.44(s, 2H), 2.72(br d, 2H), 2.41(s, 3H), 2.06(t, 2H), 1.73(br d, 2H), 1.48-1.38(m, 2H).

MP: 170°C

Example 98

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(phenylsulfanyl)acetic acid (0.118g) using the method of Example 94. Yield 0.056g as a solid.

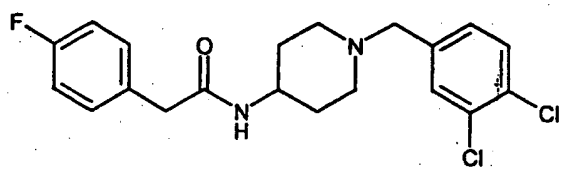
MS: APCI(+ve) 409 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.00(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.36-7.27(m, 5H), 7.20-7.16(m, 1H), 3.61(s, 2H), 3.55-3.47(m, 1H), 3.44(s, 2H), 2.69-2.66(m, 2H), 2.02(t, 2H), 1.67-1.64(m, 2H), 1.41-1.31(m, 2H).

MP: 97-99°C

Example 99

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(4-fluorophenyl)acetic acid (0.108g) using the method of Example 94. Yield 0.15g as a solid.

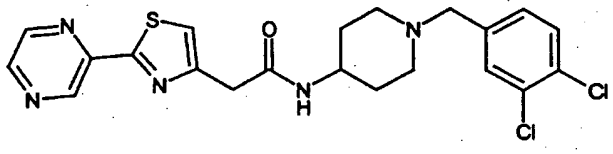
MS: APCI(+ve) 395 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.98(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.30-7.25(m, 3H), 7.13-7.07(m, 2H), 3.54-3.48(m, 1H), 3.45(s, 2H), 3.37(s, 2H), 2.72-2.69(m, 2H), 2.02(t, 2H), 1.71-1.68(m, 2H), 1.44-1.34(m, 2H).

MP: 144-7°C

Example 100

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetic acid (0.155g) using the method of Example 94. Yield 0.08g as a solid.

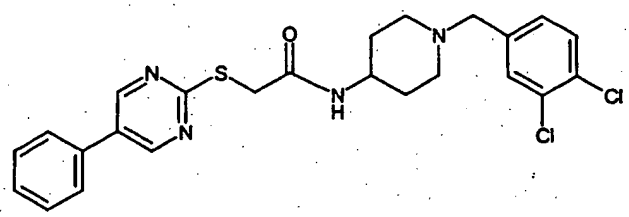
MS: APCI(+ve) 462 (M+1)

^{1}H NMR: δ (DMSO-d6) 9.25(d, 1H), 8.74-8.71(m, 2H), 8.07(d, 1H), 7.64(s, 1H), 7.59-7.54(m, 2H), 7.31-7.28(m, 1H), 3.69(s, 2H), 3.59-3.54(m, 1H), 3.45(s, 2H), 2.74-2.71(m, 2H), 2.04(t, 2H), 1.76-1.74(m, 2H), 1.49-1.39(m, 2H).

MP: 186-9°C

Example 101

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetic acid (0.172g) using the method of Example 94.
Yield 0.115g as a solid.

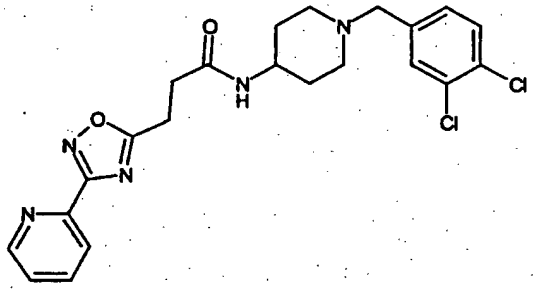
MS: APCI(+ve) 487/9 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.96(s, 2H), 8.09(d, 1H), 7.78-7.75(m, 2H), 7.58-7.43(m, 5H), 7.28(dd, 1H), 3.91(s, 2H), 3.59-3.52(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.72(br d, 2H), 1.47-1.38(m, 2H).

MP: 157°C

Example 102

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide



The title compound was prepared from the product of Example 1 step (ii) (0.9g) and 3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.3g) using the method of Example 94.
Yield 0.074g as a solid.

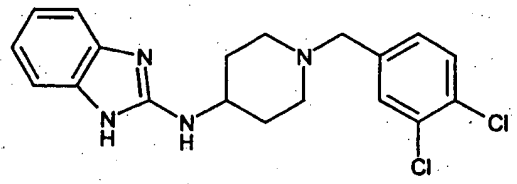
MS: APCI(+ve) 460/2 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.76-8.74(m, 1H), 8.05-7.99(m, 2H), 7.94(d, 1H), 7.61-7.56(m, 2H), 7.52(d, 1H), 7.28(dd, 1H), 3.56-3.48(m, 1H), 3.43(s, 2H), 3.19(t, 2H), 2.71-2.66(m, 4H), 2.03(t, 2H), 1.69(br d, 2H), 1.42-1.33(m, 2H).

MP: 155°C

Example 103

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine



(i) Ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate

A solution of 2-chlorobenzimidazole (1g) and ethyl 4-amino-1-piperidinecarboxylate (2g) in 1-methyl-2-pyrrolidinone was heated at 130°C for 24h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 1% triethylamine/5% methanol in dichloromethane. Yield 0.630g as a solid.

TOF MS ES+ 289.1652 (M+1)

(ii) N-(4-Piperidinyl)-1H-benzimidazol-2-amine, dihydrochloride salt

The product from step (i) (0.58g) was heated under reflux with 5M hydrochloric acid (20ml) for 24h. The solvent was evaporated under reduced pressure, the residue azeotroped with toluene, washed with ether. Yield 0.58g as a solid.

TOF MS ES+ 217.1452 (M+1)

(iii) N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine

Triethylamine (0.223ml) was added to a stirred suspension of the product from step (ii) (0.2g) in dimethylformamide. After 5min 3,4-dichlorobenzaldehyde (0.175g) then sodium triacetoxyborohydride (0.212g) was added and the mixture stirred at room temperature for 3h. The mixture was partitioned between 2M hydrochloric acid and ether, the aqueous layer was basified with aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/ether and the solid collected. Yield 0.045g.

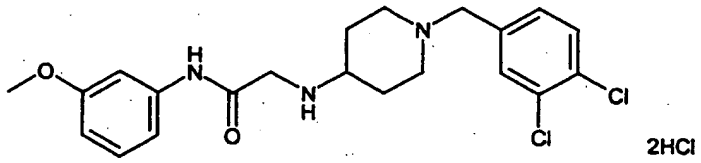
TOF MS ES+ 375.4257 (M+1)

^{1}H NMR: δ (DMSO-d6) 10.6(br s, 1H), 7.60-7.56(m, 2H), 7.32(dd, 1H), 7.12-7.09(m, 2H), 6.86-6.83(m, 2H), 6.49(d, 1H), 3.55-3.49(m, 3H), 2.79-2.71(m, 2H), 2.13-1.91(m, 4H), 1.56-1.46(m, 2H).

MP: 125°C

Example 104

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt



2-Chloro-N-(3-methoxyphenyl)-acetamide (0.241g) was added to a stirred solution of the product of Example 1 step (ii) (dihydrochloride salt) (0.4g), triethylamine (0.608g) in 1-methyl-2-pyrrolidinone (5ml). The reaction mixture was heated at 80°C for 6h then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and evaporated under reduced pressure. Purification was by chromatography eluting with chloroform/isohexane/triethylamine/methanol 30:15:3:0.5. The resulting product was converted to the hydrochloride salt using ethereal hydrogenchloride. Yield 0.135g.

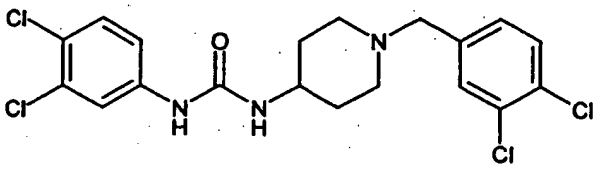
TOF MS ES+ 422.1406 (M+1)

^{1}H NMR: δ (DMSO-d6) 11.21(br s, 1H), 10.82(s, 1H), 9.53(br s, 2H), 7.95(s, 1H), 7.75(d, 1H), 7.60(d, 1H), 7.31-7.23(m, 2H), 7.15(d, 1H), 6.70(dd, 1H), 4.28(br s, 2H), 3.97(br , H), 3.73(s, 3H), 2.96(br, 2H), 2.28-2.05(m, 4H).

MP: 274-6°C

Example 105

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea



3,4-Dichlorophenyl isocyanate (0.081g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

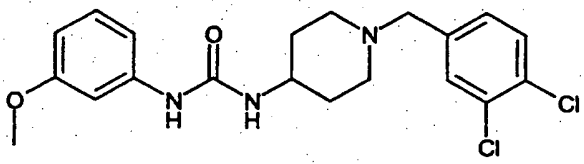
TOF MS ES+ 446.0360 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.65(s, 1H), 7.82(d, 1H), 7.59(d, 1H), 7.54(s, 1H), 7.31(d, 1H), 7.22(dd, 1H), 6.26(d, 1H), 3.45(br s , 3H), 2.67(m, 2H), 2.11(m, 2H), 1.81(m, 2H), 1.40(m, 2H).

MP: 189-190°C

Example 106

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea



3-Methoxyphenyl isocyanate (0.064g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

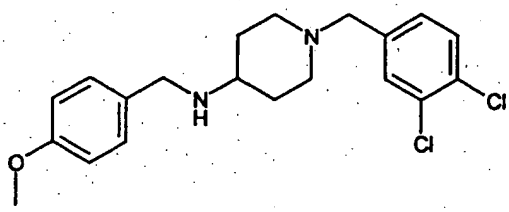
MS: APCI(+ve) 408/10 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.32(s, 1H), 7.59(d, 1H), 7.55(d, 1H), 7.31(dd, 1H), 7.13(m, 1H), 7.09(d, 1H), 6.83(dd,1H), 6.47(dd, 1H), 6.09(d, 1H), 3.69(s, 3H), 3.46(m , 3H), 2.66(m, 2H), 2.13(m, 2H), 1.81(m, 2H), 1.42(m, 2H).

MP: 178-9°C

Example 107

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt



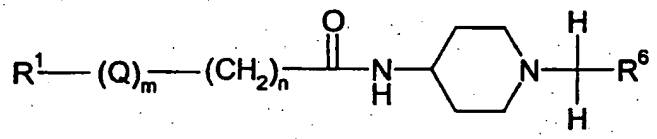
The title compound was prepared from the product of Example 1 step (ii) (0.185g) and 4-methoxybenzaldehyde (0.49ul) using the method of Example 1 step (i). Yield 0.84g as a solid.

MS: APCI(+ve) 379/81 (M+1)

^{1}H NMR: δ (DMSO-d6) 11.33(br s, 1H), 9.56(br s, 2H), 7.96 (s, 1H), 7.74(d, 1H), 7.61(d, 1H), 7.52(d, 1H), 6.97(d, 1H), 4.27(s, 2H), 4.07(s,2H), 3.77(s, 3H), 3.39-2.94(m, 5H), 2.32-2.28(m, 2H), 2.15-2.07(m, 2H).

MP: >250°C

The following table lists Examples 108-348 which are of compounds of formula (I) all of which accord to formula (Ib).



(Ib)

Example	R^1	$(Q)_m$	n	R^6
108	phenyl	m=0	2	3,4-Cl_2-C_6H_3
109	4-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
110	4-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
111	2-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
112	4-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
113	3-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
114	2-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
115	3-Cl-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
116	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
117	2-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
118	4-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3

119	3,4-$(OH)_2$-C_6H_3	m=0	2	3,4-Cl_2-C_6H_3
120	4-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
121	phenyl	m=0	4	3,4-Cl_2-C_6H_3
122	3,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
123	3-F-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
124	3,4-methylenedioxyphenyl	m=0	1	3,4-Cl_2-C_6H_3
125	4-OH-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
126	4-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
127	4-phenyl-phenyl	m=0	1	3,4-Cl_2-C_6H_3
128	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
129	3-OH-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
130	4-CH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
131	4-NO_2-C_6H_4	m=0	3	3,4-Cl_2-C_6H_3
132	3,4-$(OCH_3)_2$-C_6H_3	m=0	2	3,4-Cl_2-C_6H_3
133	C_6F_5	m=0	2	3,4-Cl_2-C_6H_3
134	4-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
135	4-OCF_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
136	3,4-$(OCH_3)_2$-C_6H_3	m=0	3	3,4-Cl_2-C_6H_3
137	4-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
138	4-$N(CH_3)_2$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
139	4-OCH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
140	3,4,5-$(OCH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
141	3,4-methylenedioxyphenyl	m=0	2	3,4-Cl_2-C_6H_3
142	3-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
143	naphth-1-yl	m=0	1	3,4-Cl_2-C_6H_3
144	3-OCH_3-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
145	3-(6-Br-1-(prop-2-en-1-yl)-naphth-2-yloxymethyl)phenyl	m=0	1	3,4-Cl_2-C_6H_3
146	4-(4-NO_2-C_6H_4-CH_2O)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3

147	3-F-4-CH_3O-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
148	3-CH_3-C_6H_4	m=0	4	3,4-Cl_2-C_6H_3
149	3-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
150	4-(C_6H_5-CH_2O)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
151	4-(3-NO_2-C_6H_4)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
152	2,5-$(CH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
153	4-I-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
154	3-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
155	2-CH_3-3-NO_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
156	3-OH-4-OCH_3-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
157	3-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
158	2-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
159	3,5-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
160	3-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
161	phenyl	m=0	1	3,4-Cl_2-C_6H_3
162	3,5-$(CH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
163	3-OCH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
164	2,4-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
165	2-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
166	3,4-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
167	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
168	Pyridin-3-yl	m=0	1	3,4-Cl_2-C_6H_3
169	Pyridin-2-yl	m=0	1	3,4-Cl_2-C_6H_3
170	5-Br-pyridin-3-yl	m=0	1	3,4-Cl_2-C_6H_3
171	2,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
172	4-(benzyloxy)phenyl	m=0	1	3,4-Cl_2-C_6H_3
173	3-(benzyloxy)phenyl	m=0	1	3,4-Cl_2-C_6H_3
174	2-methyl-naphth-1-yl	m=0	1	3,4-Cl_2-C_6H_3
175	2-CH_3CH_2O-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
176	3,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
177	4-$CH_3(CH_2)_3O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3

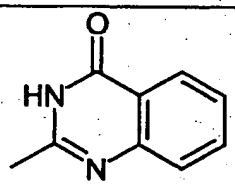
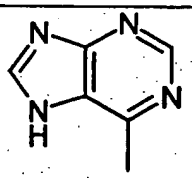
178	Indol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
179	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
180	Thien-2-yl	m=0	1	3,4-Cl_2-C_6H_3
181	3-Cl-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
182	2,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
183	2,6-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
184	2-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
185	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
186	3-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
187	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
188	3-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
189	2-($ClCH_2C(O)NH$)-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
190	3-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
191	2,5-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
192	4-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
193	Indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
194	5-OCH_3-indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
195	Naphth-2-yl	m=0	1	3,4-Cl_2-C_6H_3
196	4-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
197	3,4,5-$(OCH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
198	4-$CH_3(CH_2)_3O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
199	4-$S(O)_2CH_3$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
200	2,4,6-$(CH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
201	4-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
202	2-(pyrazin-2-yl)-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
203	2-CH_3-5-$(CH_3)_2CH$-indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
204	5-(pyrrolidin-1-yl)-tetrazol-2-yl	m=0	1	3,4-Cl_2-C_6H_3

205	5-(4-CH_3-phenyl)-tetrazol-2-yl	m=0	1	3,4-Cl_2-C_6H_3
206	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
207	3-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
208	5-Cl-benzo[b]thiophen-3-yl	m=0	1	3,4-Cl_2-C_6H_3
209	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
210	2-phenyl-5-methyl-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
211	4-OCF_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
212	3-methyl-5-Cl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl_2-C_6H_3
213	3-methyl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl_2-C_6H_3
214	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
215	3-NO_2-1,2,4-triazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
216	3,4-$(NO_2)_2$-5-CH_3-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
217	4-$(CH_3)_2CH(CH_2)_2O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
218	2,3-$(CH_3)_2$-indol-5-yl	m=0	1	3,4-Cl_2-C_6H_3
219	3,5-$(CH_3)_2$-4-Cl-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
220	3,5-$(CH_3)_2$-4-NO_2-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
221	2,4-$(NO_2)_2$-imidazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
222	4-NO_2-imidazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
223	3,5-$(CH_3)_2$-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
224	4-$CH_3(CH_2)_5$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
225	2-CN-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
226	4-Cl-C_6H_4	O	1	4-Cl-C_6H_4
227	4-Cl-C_6H_4	O	1	2-Br-C_6H_4

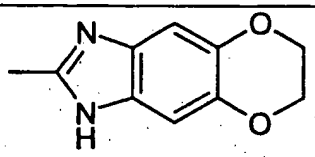
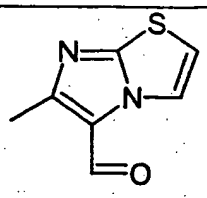
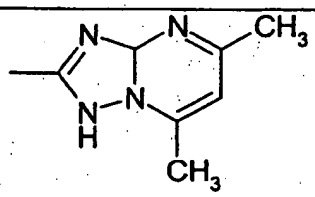
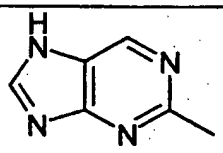
228	4-Cl-C_6H_4	O	1	3-(CO_2CH_3)-4-Br-C_6H_4
229	4-Cl-C_6H_4	O	1	4-NO_2-C_6H_4
230	4-Cl-C_6H_4	O	1	3-benzoyl-phenyl
231	4-Cl-C_6H_4	O	1	5-OCH_3-benzimidazol-2-yl
232	4-Cl-C_6H_4	O	1	4-Br-C_6H_4
233	4-Cl-C_6H_4	O	1	4-(1,2,3-thiadiazol-4-yl)-phenyl
234	4-Cl-C_6H_4	O	1	4-CH_3-C_6H_4
235	4-Cl-C_6H_4	O	1	4-(2,6-Cl_2-C_6H_3)$CH_2S(O)_2$-C_6H_4
236	4-Cl-C_6H_4	O	1	3,5-Br_2-C_6H_3
237	4-Cl-C_6H_4	O	1	Indan-5-yl
238	4-Cl-C_6H_4	O	1	2-F-3-Cl-C_6H_3
239	4-Cl-C_6H_4	O	1	benzofurazan-5-yl
240	4-Cl-C_6H_4	O	1	7-Cl-quinolin-2-yl
241	4-F-C_6H_4	m=0	1	2,5-Cl_2-C_6H_3
242	4-F-C_6H_4	m=0	1	2,3-Cl_2-C_6H_3
243	4-F-C_6H_4	m=0	1	4-F-C_6H_4
244	4-F-C_6H_4	m=0	1	3-CO_2CH_3-4-Br-C_6H_3
245	4-F-C_6H_4	m=0	1	4-NO_2-C_6H_4
246	4-F-C_6H_4	m=0	1	3-benzoyl-phenyl
247	4-F-C_6H_4	m=0	1	4-CH_3-naphth-1-yl
248	4-F-C_6H_4	m=0	1	3,4-methylene-dioxyphenyl
249	4-F-C_6H_4	m=0	1	5-OCH_3-benzimidazol-2-yl
250	4-F-C_6H_4	m=0	1	3-NO_2-4-CH_3-

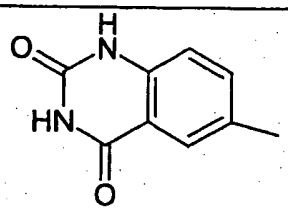
				C_6H_3
251	4-F-C_6H_4	m=0	1	3,4-$(CH_3)_2$-C_6H_3
252	4-F-C_6H_4	m=0	1	3-CH_3-4-OCH_3-C_6H_3
253	4-F-C_6H_4	m=0	1	4-(2-C(O)NH_2-C_6H_4)-C_6H_4
254	4-F-C_6H_4	m=0	1	4-Br-C_6H_4
255	4-F-C_6H_4	m=0	1	4-(2,6-Cl_2-C_6H_4)$CH_2S(O)_2$-C_6H_4
256	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Cl-C_6H_4
257	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-4-OCH_3-C_6H_3
258	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	2,3-Cl_2-C_6H_3
259	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-F-C_6H_4
260	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CF_3-C_6H_4
261	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-NO_2-C_6H_4
262	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-benzoyl-phenyl
263	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-methylene-dioxyphenyl
264	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,5-$(CH_3)_2$-C_6H_3
265	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-NO_2-4-CH_3-C_6H_3
266	3-(pyridin-2-yl)-1,2,4-	m=0	2	3,4-$(CH_3)_2$-C_6H_3

	oxadiazol-5-yl			
267	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH_3-C_6H_4
268	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH_3-4-OCH_3-C_6H_4
269	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Br-C_6H_4
270	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Indan-5-yl
271	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF_3-C_6H_4
272	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Naphth-2-yl
273	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH_3-C_6H_4
274	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	benzofurazan-5-yl
275	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-F_2-C_6H_3
276	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	7-Cl-quinolin-2-yl
277	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-C_6H_4
278	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF_3-C_6H_4
279	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH_3-C_6H_4
280	4-OCH_3-C_6H_4	O	1	3,4-Cl_2-C_6H_3
281	4-Cl-C_6H_4	O	1	3,4-Cl_2-C_6H_3
282	4-NO_2-C_6H_4	O	1	3,4-Cl_2-C_6H_3
283	4-NHC(O)CH_3-C_6H_4	O	1	3,4-Cl_2-C_6H_3

284	4-O$(CH_2)_2CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
285	3-$CO_2CH_2CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
286	2-$C(CH_3)_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
287	2-NHC(O)CH_3-C_6H_4	O	1	3,4-Cl_2-C_6H_3
288	3,5-$(OCH_3)_2$-C_6H_3	O	1	3,4-Cl_2-C_6H_3
289	2-OCH_3-5-NO_2-C_6H_3	O	1	3,4-Cl_2-C_6H_3
290	4-CN-C_6H_4	O	1	3,4-Cl_2-C_6H_3
291	2-Cl-5-CF_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
292	2-NO_2-5-CH_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
293	3-Cl-5-OCH_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
294	3-NO_2-C_6H_4	O	1	3,4-Cl_2-C_6H_3
295	3-Br-C_6H_4	O	1	3,4-Cl_2-C_6H_3
296	4-I-C_6H_4	O	1	3,4-Cl_2-C_6H_3
297	3,5-F_2-C_6H_3	O	1	3,4-Cl_2-C_6H_3
298	4,6-$(NH_2)_2$-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
299	Benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
300	Thiazol-2-yl	S	1	3,4-F_2-C_6H_3
301		S	1	3,4-F_2-C_6H_3
302	5-NO_2-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
303	Pyridin-2-yl	S	1	3,4-F_2-C_6H_3
304		S	1	3,4-F_2-C_6H_3
305	1H-1,2,4-triazol-3-yl	S	1	3,4-F_2-C_6H_3
306	Pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
307	1-phenyl-tetrazol-5-yl	S	1	3,4-F_2-C_6H_3
308	4,6-$(CH_3)_2$-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3

309	4-(thiophen-2-yl)-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
310	2-(cyclopropyl-CH_2S)-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3
311	4-methyl-3-(thiophen-2-yl)-1,2,4-triazol-5-yl	S	1	3,4-F_2-C_6H_3
312	3-CN-6-($CH_3C(O)$)-pyridin-2-yl	S	1	3,4-F_2-C_6H_3
313	1H-pyrazolo[3,4-d]pyrimidin-4-yl	S	1	3,4-F_2-C_6H_3
314	5-OCH_3-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
315	5-F-6-Cl-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
316	4,5-dihydrothiazol-2-yl	S	1	3,4-F_2-C_6H_3
317	1H-5-phenyl-1,2,4-triazol-3-yl	S	1	3,4-F_2-C_6H_3
318	2-(thiophen-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F_2-C_6H_3
319	Quinoxalin-2-yl	S	1	3,4-F_2-C_6H_3
320	2,5-Cl_2-C_6H_3	S	1	3,4-F_2-C_6H_3
321	2-(pyridin-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F_2-C_6H_3
322	7-CF_3-quinolin-4-yl	S	1	3,4-F_2-C_6H_3
323	2-(pyridin-2-yl)-4-CH_3-pyrimidin-6-yl	S	1	3,4-F_2-C_6H_3
324	Naphth-1-yl	S	1	3,4-F_2-C_6H_3
325	3,4-$(OCH_3)_2$-C_6H_3	S	1	3,4-F_2-C_6H_3
326	1,3,4-thiadiazol-2-yl	S	1	3,4-F_2-C_6H_3
327	3-CF_3-C_6H_4	S	1	3,4-F_2-C_6H_3

328		S	1	3,4-F_2-C_6H_3
329	3,4-Cl_2-C_6H_3	S	1	3,4-F_2-C_6H_3
330	3-CN-5-CH_3-pyridin-2-yl	S	1	3,4-F_2-C_6H_3
331	4-phenyl-thiazol-2-yl	S	1	3,4-F_2-C_6H_3
332		S	1	3,4-F_2-C_6H_3
333	2-CH_3-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3
334		S	1	3,4-F_2-C_6H_3
335		S	1	3,4-F_2-C_6H_3
336	2-phenoxy-phenyl	S	1	3,4-F_2-C_6H_3
337	2-OCH_3-C_6H_4	S	1	3,4-F_2-C_6H_3
338	2-CH_3-4-Cl-C_6H_3	S	1	3,4-F_2-C_6H_3
339	2-CH_3-6-Cl-C_6H_3	S	1	3,4-F_2-C_6H_3
340	2-(HC≡C-CH_2S)-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3
341	2-CO_2CH_3-C_6H_4	S	1	3,4-F_2-C_6H_3
342	4-CN-C_6H_4	O	1	3,4-F_2-C_6H_3
343	4-($(CH_3)_2NCH_2$)-C_6H_4	O	1	3,4-F_2-C_6H_3

344		O	1	3,4-F_2-C_6H_3
345	3-CH_2OH-C_6H_4	O	1	3,4-F_2-C_6H_3
346	2-OCH_2CH_2OH-C_6H_4	O	1	3,4-F_2-C_6H_3
347	4-$CH_3(CH_2)_2O$-C_6H_4	O	1	3,4-F_2-C_6H_3
348	3-Cl-5-OCH_3-C_6H_3	O	1	3,4-F_2-C_6H_3

General Preparation of Examples 108-225

PyBroP® (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 2 equivalents) was added to a solution of the product from Example 1 step (ii) (hydrochloride salt, 1mg) the appropriate acid (2 equivalents) and triethylamine in 1-methyl-2-pyrrolidone (0.2ml) and was left for 24h. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.3ml).

General Preparation of Examples 225-240

Step i: *tert*-Butyl 4-{[(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate

Prepared following the method of Example 94 using (4-chlorophenoxy)acetic acid (0.50g), 1,1-carbonyldiimidazole (0.50g) and *tert*-butyl 4-amino-1-piperidinecarboxylate (0.46g) to give the subtitle compound (0.54g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.34 – 1.40 (2H, m), 1.46 (9H, s), 1.90 – 1.95 (2H, m), 2.86 – 2.88 (2H, m), 4.01 – 4.14 (3H, m), 4.45 (2H, s), 6.38 – 6.41 (1H, m), 6.84 – 6.87 (2H, m), 7.26 – 7.30 (2H, m).

Step ii: 2-(4-chlorophenoxy)-*N*-(4-piperidinyl)acetamide

Prepared following the method of Example 1 step (ii) using *tert*-butyl 4-{[(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate (0.52g) to give the subtitle compound (0.35g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.32 – 1.45 (2H, m), 1.93 – 1.97 (2H, m), 2.68 – 2.77 (2H, m), 3.07 – 3.11 (2H, m), 3.91 – 4.04 (1H, m), 4.45 (2H, s), 6.38 – 6.40 (1H, m), 6.84 – 6.89 (2H, m), 7.26 – 7.31 (2H, m).

Step iii: Final product

A mixture of the product from step (ii) (1.07mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 241-255

A mixture of 2-(4-fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.94mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 256-279

Step i: *tert*-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.60g) was dissolved in dichloromethane (10ml). 1,1-Carbonyldiimidazole (0.33g) was added followed by *tert*-butyl 4-amino-1-piperidinecarboxylate hydrochloride (0.5g) and triethylamine (0.31ml). After 2hours water, brine and dichloromethane were added and the phases separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate : methanol (33:1) to give the subtitle compound (0.40g).

^{1}H NMR (399.98 MHz, DMSO) δ 1.22 – 1.24 (2H, m), 1.39 (9H, s), 1.62 - 1.71 (2H, m), 2.66 - 2.71 (4H, m), 3.18 - 3.23 (2H, m), 3.65 - 3.83 (3H, m), 7.58 - 7.63 (1H), 8.01 - 8.04 (3H, m), 8.74 - 8.76(1H, m).

Step ii: *N*-(4-Piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

tert-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate (0.40g) was dissolved in dichloromethane (6ml) and trifluoroacetic acid (3ml) was added. After 2hours water, 2N sodium hydroxide and dichloromethane were added and the phases were separated. The organic phase was dried, filtered and evaporated to give the subtitle compound (0.19g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.35 – 1.45 (2H, m), 1.86 – 1.97 (2H, m), 2.69 – 2.84 (4H, m), 3.09 – 3.13 (2H, m), 3.32 – 3.36 (2H, m), 3.86 – 3.95 (1H, m), 5.82 – 5.84 (1H, m), 7.42 - 7.45 (1H, m), 7.83 – 7.87 (1H, m), 8.10 – 8.12 (1H, m), 8.78 – 8.79 (1H, m).

Step iii: Final product

A mixture of the product from step (ii) (1.21mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 280-296

Step i: 2-Chloro-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Prepared following the general preparation method of Examples 297-357 step (iii) using 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (2.0g), *N,N*-diisopropylethylamine (5.55 ml) and chloroacetyl chloride (0.55ml) to give the subtitle compound (1.0g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.48 – 1.61 (2H, m), 1.91 – 1.94 (2H, m), 1.95 – 2.18 (2H, m), 2.77 – 2.80 (2H, m), 3.44 (2H, s), 3.78 – 3.87 (1H, m), 4.04 (2H, s), 7.13 – 7.16 (1H, m), 7.37 – 7.43 (2H, m).

Step ii: Final Product

A mixture of the product from step (i) (1.34 mg), the appropriate phenol (1.5 equivalents) and potassium *tert*-butoxide (1.4 equivalents) in 1-methyl-2-pyrrolidinone (0.13ml) was left at room temperature for 24hours. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 297-340

Step i: Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester

Carbamic acid, 4-piperidinyl-, 1,1-dimethylethyl ester (6.95g) was dissolved in *N,N*-dimethylformamide (70ml). 3,4-Difluorobenzylbromide (4.55ml) and potassium carbonate (16.0g) were added. The mixture was heated to reflux for 16hours, then allowed to cool to room temperature. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate. The organic phases were washed with water (twice) and brine,

then dried, filtered and evaporated. The residue was triturated with ether : *iso*-hexane (1:1) to give the subtitle compound (8.13g)

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.36 - 1.43 (m, 2H), 1.44 (s, 9H), 1.91 (d, J = 11.8 Hz, 2H), 2.08 (td, J = 11.4, 2.7 Hz, 2H), 2.75 (d, J = 11.3 Hz, 2H), 3.41 (s, 2H), 3.42 - 3.55 (m, 1H), 4.38 - 4.47 (m, 1H), 6.96 - 7.02 (m, 1H), 7.04 - 7.11 (m, 2H), 7.13 - 7.19 (m, 1H)

Step ii: 1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride

Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester was suspended in 6N hydrochloric acid (100ml). After 16hours excess hydrochloric acid was evaporated and the residue azeotroped with toluene, dried and evaporated to give the subtitle compound (8.10g).

^{1}H NMR (399.98 MHz, DMSO) δ 1.91-2.01(2H,m), 2.31-2.47(2H,m), 2.86-3.20(2H,m), 3.54-3.66(3H,m), 4.75-4.83(2H,s), 7.26-7.61(3H,m).

Step iii: 2-Chloro-*N*-[1-[(3,4-difluorophenyl)methyl]-piperidin-4-yl]-acetamide

1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride (3.18g) was dissolved in tetrahydrofuran (40ml). Diisopropylethylamine (6.84g) and chloroacetyl chloride (1.33g) were added. After 3hours water, brine and ethyl acetate were added the phase were separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate to give the subtitle compound (0.728g).

^{1}H NMR ($CDCl_3$) δ 1.46 – 1.59 (2H, m), 1.93 (2H, dt), 2.14 (2H, td), 2.78 (2H, d), 3.43 (2H, s), 3.76 – 3.91 (1H, m), 4.04 (2H, s), 6.39 – 6.51 (1H, m), 6.98 – 7.02 (1H, m), 7.08 (1H, dd), 7.17 (1H, ddd).

Step iv: Final Product

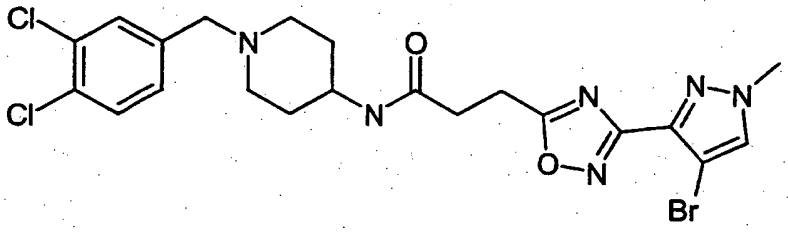
The product from step (iii) (1.21mg) was dissolved in dimethylsulfoxide (50μl) and diisopropylethylamine (1.55mg, 3 equivalents) was added as a solution in dimethylsulfoxide (50μl). The appropriate thiol was added (1 equivalent) in dimethylsulfoxide (40μl) and the reaction mixture was left at room temperature for 24hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (400μl).

General Preparation of Examples 341-348

Prepared from the product of general preparation for Examples 297-340 step (iii) and the appropriate phenol following the method of Examples 280-296 step (ii).

Example 351

3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



Step i: Methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (3.50g) in dichloromethane (100ml) was added methyl 4-chloro-4-oxobutanoate (2.00g) dropwise. Triethylamine (3.90g) was added and the reaction stirred under nitrogen for 2 hours. Saturated sodium hydrogen carbonate solution was then added, with the solution being extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over anhydrous magnesium sulfate. After filtration the solvent was removed under reduced pressure to leave methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.00g).

MS (+veES) 373 ($(M+H)^+$)

Step ii: Lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.72g) in methanol (30ml) was added lithium hydroxide (0.41g) in water (10ml) which was stirred under nitrogen for 48 hours. The solvent was removed under reduced pressure, the residue was triturated with ether and filtered to leave lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.50g).

MS (+veES) 359 ($(M+H)^+$)

Step iii: 3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide

To lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (0.292g) in dichloromethane (6ml) was added dimethylformamide (1.5ml), 1-(3-

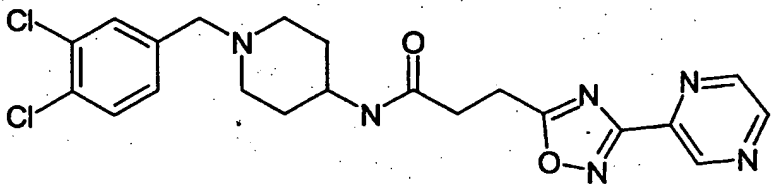
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), 4-bromo-*N*'-hydroxy-1-methyl-1*H*-pyrazole-3-carboximidamide (0.175g) and triethylamine (0.161g). Reaction was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure, followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by reverse phase hplc (RPHPLC; 75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the titled compound (0.164g).

MS (+veAPC) 543 ($(M+H)^+$)

^{1}H NMR (DMSO): δ 8.21-8.17(1H,m); 7.95-7.76(1H,m); 7.60-7.54(1H,m); 7.35-7.25(1H,m); 4.35-4.21(1H,m); 3.93(2H,s); 3.44-3.35(2H,m); 3.19-3.14(3H,m); 2.73-2.64(2H,m); 2.58(3H,s); 2.00-1.89(2H,m); 1.73-1.60(2H,m); 1.36-1.24(1H,m).

Example 352

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]propanamide



To lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (Example 351, step ii) (0.292g) in dichloromethane (6ml) was added *N*,*N*-dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), *N*'-hydroxy-2-pyrazinecarboximidamide (0.110g) and triethylamine (0.161g). The reaction mixture was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried

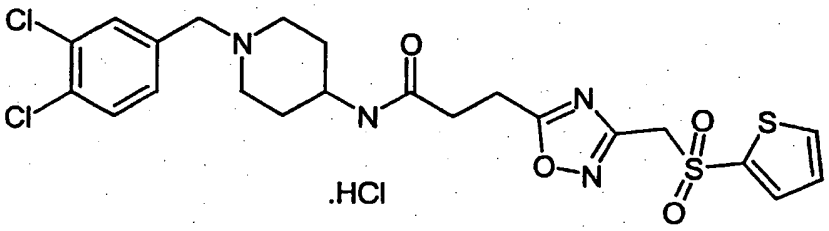
over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the title compound (0.067g).

MS (+veAPC) 461 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 9.23(1H,s); 8.81-8.45(2H,m); 7.96-7.94(1H,m); 7.58-7.56(1H,m); 7.53-7.52(1H,m); 7.29-7.26(1H,m); 3.55-3.48(1H,m); 3.43(2H,s); 3.24-3.20(2H,m); 2.71-2.68(4H,m); 2.03-1.98(2H,m); 1.70-1.68(2H,m); 1.42-1.33(2H,m).

Example 353

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride



Step i: 3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (1*Z*)-*N*'-hydroxy-2-(2-thienylsulfonyl)ethanimidamide (0.250g) with dihydro-2,5-furandione (0.114g) in dimethylformamide (0.2ml) was heated at 120°C for 2 hours. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave 3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g).

MS (+veES) 303 ($(M+H)^+$)

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride

3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g) in dichloromethane was stirred under nitrogen. Oxalyl chloride (0.252g) was added dropwise followed by the addition of one drop of dimethylformamide. After 30 minutes the solvent and oxalyl chloride was removed under reduced pressure followed by the addition of dichloromethane (10ml), 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.347g), and triethylamine (0.202g) and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once

with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a brown oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile) followed by chromatography using 3% ethanol/ dichloromethane. The solvent was removed under reduced pressure, followed by the addition of hydrogen chloride in diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride (0.04g) as a pale yellow solid.

MS (+veES) 545 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 10.51(1H,s); 8.21-8.13(2H,m); 7.91(1H,s); 7.77-7.71(2H,m); 7.58-7.55(1H,m); 7.28-7.26(1H,m); 5.07-5.05(2H,m); 4.26-4.25(2H,m); 3.92(1H,m); 3.34-3.31(2H,m); 3.15-3.08(2H,m); 3.02-2.94(2H,m); 2.60-2.58(2H,m); 1.92-1.84(2H,m); 1.80-1.70(2H,m).

Example 354

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: 3-[3-(4-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid

N'-hydroxy-4-pyridinecarboximidamide (0.300g) with dihydro-2,5-furandione (0.217g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with ethanol and filtered to leave 3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.241g).

MS (+veES) 220 ($(M+H)^+$)

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

For method refer to Example 353 step ii.

Purification was performed via chromatography (2.5% ethanol/ dichloromethane). Solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (0.154g) as a pale cream solid.

MS (+veES) 460 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.81-8.79(2H,m); 7.96-7.90(3H,m); 7.60-7.56(2H,m); 7.30-7.27(1H,m); 3.53-3.51(1H,m); 3.44(2H,s); 3.23-3.19(2H,m); 2.71-2.68(4H,m); 2.05-1.97(2H,m); 1.71-1.67(2H,m); 1.44-1.32(2H,m).

Example 355

Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Step i: Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid *N*'-hydroxy-2-pyridinecarboximidamide (0.137g) with 3-oxabicyclo[3.1.0]hexane-2,4-dione (0.112g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.200g).

MS (+veES) 232 ($(M+H)^+$)

Step ii: Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.139g) and N,N'-carbonyldiimidazole (0.110g)in dichloromethane was stirred under nitrogen for 1 hour. 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.198g), and triethylamine (0.121g) was then added and allowed to stir for 24 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). The solvent was removed under reduced pressure to leave Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide (0.054g) as a white solid.

MS (+veES) 472 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.74-8.73(1H,m); 8.26-8.24(1H,m); 8.03-7.98(2H,m); 7.59-7.55(2H,m); 7.51(1H,s); 7.27-7.25(1H,m); 3.44-3.37(3H,m); 2.67-2.63(3H,m); 2.27-2.21(1H,m); 2.00-1.89(2H,m); 1.66-1.65(2H,m); 1.59-1.56(1H,m); 1.48-1.43(1H,m); 1.37-1.32(2H,m).

Example 356

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

Step i: 3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid

2-Pyridinecarbohydrazonamide (0.136g) and dihydro-2,5-furandione (0.100g) in 1 ml of dimethylacetamide was heated for 10 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W under nitrogen to leave 3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid in 1ml of dimethylacetamide.

MS (-veES) 217 ($(M-H)^+$)

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid (0.218g in 1ml dimethylacetamide) and N,N'-carbonyldiimidazole (0.250g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.316g), and triethylamine (0.218g) was then added and allowed to stir for 2 hours under nitrogen. 1M sodium hydroxide was added to the reaction with the resulting solution being washed three times with dichloromethane. The aqueous phase was acidified with glacial acetic acid, with the water/ acetic acid being removed under reduced pressure. Water was then added and extracted three times with dichloromethane. The pooled organic phases were extracted once with water and the water removed under reduced pressure to leave a white solid. This was then triturated with diethyl ether/ dichloromethane, filtered and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), solvent removed to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide (0.02g).

MS (+veES) 459 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.66-8.65(1H,m); 8.03-8.01(1H,m); 7.95-7.91(1H,m); 7.83-7.81(1H,m); 7.58-7.56(1H,m); 7.52(1H,m); 7.47-7.44(1H,m); 7.29-7.27(1H,m); 3.55-3.50(1H,m); 3.43(2H,s); 2.93-2.89(2H,m); 2.68-2.67(2H,m); 2.55-2.49(2H,m); 2.04-1.98(2H,m); 1.70-1.68(2H,m); 1.42-1.32(2H,m).

Example 357

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide (3-Phenyl-1*H*-1,2,4-triazol-5-yl)acetic acid (0.020g) and N,N'-carbonyl diimidazole (0.016g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.031g) and triethylamine (0.036g) was then added and allowed to stir for 1 hour under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to a white solid. This was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Saturated sodium hydrogen carbonate was added to the pooled collected fractions with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide(0.031g).

MS (+veES) 444 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.18-8.15(1H,m); 7.98-7.95(2H,m); 7.59-7.54(2H,m); 7.49-7.41(3H,m); 7.31-7.29(1H,m); 3.63(2H,s); 3.57-3.47(1H,m); 3.45(2H,s); 2.74-2.70(2H,m); 2.08-2.01(2H,m); 1.77-1.74(2H,m); 1.48-1.38(2H,m).

Example 358

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)propanoic acid (0.175g) and N,N'-carbonyldiimidazole (0.148g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.263g), and triethylamine (0.126g) was then added and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was purified by chromatography using 2.5% ethanol/ dichloromethane. The solvent was removed under reduced pressure and was

purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), followed by 1 ml of glacial acetic acid being added and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate (0.024g).

MS (+veES) 445 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.31-8.29(1H,m); 7.98-7.96(2H,m); 7.66-7.54(5H,m); 7.31-7.29(1H,m); 3.92(2H,s); 3.57-3.56(1H,m); 3.46(2H,s); 2.74-2.71(2H,m); 2.07-2.02(2H,m); 1.78-1.75(2H,m); 1.47-1.39(2H,m).

Example 359

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Step i: Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate

2-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridine (0.150g) was stirred at -78°C in dry tetrahydrofuran under nitrogen. (1.6M) *n*-butyl lithium (0.757ml) was added dropwise so as to maintain the temperature at -78°C. After 30 minutes carbon dioxide was passed through the solution and the reaction was allowed to return to room temperature. Once the reaction had reached room temperature, water (1ml) was added and all solvents were removed under reduced pressure to leave a yellow solid. This solid was triturated with ethyl acetate and filtered to leave a pale yellow solid (0.150g).

^{1}H NMR (DMSO+D_2O) δ 8.75-8.73(1H,m); 8.12-8.00(2H,m); 7.65-7.61(1H,m); 3.77(2H,s).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate (0.140g), 1-(3,4-dichlorobenzyl)-4-piperidinamine (0.170g), PyBroP™ (0.400g) were stirred under nitrogen in dimethylformamide (15ml). N,N-Diisopropylethylamine (0.171g) was added and left to stir for 2 hours. 1M sodium hydroxide was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave product plus dimethylformamide. Water was added which resulted in precipitation of the product. The product was filtered

and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). After removal of the solvent under reduced pressure the resulting white solid was triturated with diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide (0.067g).

m.p. 145°C

MS (+veES) 446 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.77-8.75(1H,m); 8.37-8.35(1H,m); 8.07-8.00(2H,m); 7.62-7.54(3H,m); 7.31-7.30(1H,m); 4.02(2H,s); 3.60-3.55(1H,m); 3.46(2H,s); 2.74-2.67(2H,m); 2.08-2.03(2H,m); 1.78-1.76(2H,m); 1.48-1.39(2H,m).

Example 360

N-[1-(4-Bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 1.00g), 1-bromo-4-(bromomethyl)benzene (1.06g) and potassium carbonate (0.877g) in dimethylformamide (15ml) were heated to 70°C, under nitrogen for 1 hour. Water was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was triturated with diethyl ether, filtered and recrystallised from ethanol/ water to give white crystalline needles of *N*-[1-(4-bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide.

m.p. 144°C

MS (+veES) 407 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 7.99-7.98(1H,m); 7.51-7.49(2H,m); 7.28-7.24(4H,m); 7.12-7.06(2H,m); 3.51-3.46(1H,m); 3.41(2H,s); 3.36(2H,s); 2.72-2.69(2H,m); 2.01-1.96(2H,m); 1.70-1.68(2H,m); 1.42-1.34(2H,m).

Example 361

2-(4-Fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.05g), 2-quinolinecarbaldehyde (0.033g) and sodium triacetoxyborohydride (0.067g) in dichloroethane (3ml) were stirred under nitrogen for 24 hours. Saturated sodium hydrogen

carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with diethyl ether/ ethyl acetate and filtered to leave 2-(4-fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide (0.020g).

MS (+veES) 378 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.34-8.31(1H,m); 8.02-7.94(3H,m); 7.75-7.71(1H,m); 7.63-7.55(2H,m); 7.28-7.25(2H,m); 7.13-7.08(2H,m); 3.74(2H,s); 3.57-3.50(1H,m); 3.30(2H,s); 2.79-2.76(2H,m); 2.16-2.11(2H,m); 1.73-1.70(2H,m); 1.48-1.39(2H,m).

Example 362

N-[1-(3-Chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.218g) and N,N'-carbonyldiimidazole (0.194g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(3-Chloro-4-fluorobenzyl)-4-piperidinamine (JP 59101483; 0.242g) was then added and left to stir for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with ethyl acetate/ ethanol and filtered to leave *N*-[1-(3-chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide.

m.p. 150°C

MS (+veAPC) 444 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.75-8.74(1H,m); 8.05-7.99(2H,m); 7.95-7.93(1H,m); 7.61-7.58(1H,m); 7.48-7.45(1H,m); 7.37-7.30(1H,m); 7.30-7.26(1H,m); 3.53-3.51(1H,m); 3.42(2H,s); 3.21-3.17(2H,m); 2.71-2.66(4H,m); 2.02-1.96(2H,m); 1.70-1.67(2H,m); 1.42-1.33(2H,m).

Example 363

N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: *tert*-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate

4-Chloro-3-fluorobenzaldehyde (0.793g) and *tert*-butyl 4-piperidinylcarbamate (1.00g) were stirred under nitrogen in dried tetrahydrofuran (25ml). Sodium triacetoxyborohydride (1.266g) was then added and left for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *tert*-butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) as a white solid.

MS (+veAPC) 343 ($(M+H)^+$)

Step ii: 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine

tert-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) in dichloromethane (20ml) was stirred under nitrogen. Trifluoroacetic acid (5ml) was then added dropwise and the reaction was left to stir for 2 hours. 1M sodium hydroxide was added to the reaction until basic, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Product purified by chromatography (5% ethanol/ dichloromethane to 10% ethanol/ dichloromethane) and solvent removed under reduced pressure to leave an oil which crystallised over the period of 48 hours. The resulting solid was triturated with diethyl ether and filtered to leave 1-(4-chloro-3-fluorobenzyl)-4-piperidinamine (0.500g) as a white solid.

Step iii: N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.136g) and N,N'-carbonyldiimidazole (0.114g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine (0.150g) was then added and left to stir for 2 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This was triturated with diethyl ether which caused product the to crystallise. After filtration, the product was

washed with diethyl ether and dried to N-[1-(4-chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide.

m.p. 132°C

MS (+veES) 444 ($(M+H)^+$)

^{1}H NMR (DMSO) δ 8.76-8.74(1H,m); 8.05-7.99(2H,m); 7.95-7.94(1H,m); 7.61-7.58(1H,m); 7.54-7.50(1H,m); 7.32-7.28(1H,m); 7.16-7.14(1H,m); 3.55-3.47(1H,m); 3.44(2H,s); 3.21-3.17(2H,m); 2.71-2.66(4H,m); 2.03-1.97(2H,m); 1.70-1.67(2H,m); 1.42-1.33(2H,m).

Example 364

2-(4-Chlorophenoxy)-N-[1-[(3,4-dichlorophenyl)methyl]-piperidin-4-yl]-acetamide

The product from Example 1 step (ii) was dissolved in dichloromethane (10ml) containing triethylamine (0.081g) and the solution was cooled to 0°C. 4-Chlorophenoxyacetyl chloride (88mg) in dichloromethane (3ml) was added dropwise, the cooling bath was removed and the resulting solution was stirred for 1hour. Ethyl acetate, water and brine were added and the phases were separated. The organic phase was dried, filtered and evaporated to give an oil which was purified by reverse phase HPLC (with a gradient eluent system (25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN/NH_4OAc_{aq} (0.1%)) to give the title compound (0.049g).

^{1}H NMR: ($CDCl_3$): δ 1.51 (2H, ddd), 1.89 - 1.96 (2H, m), 2.15 (2H, td), 2.77 (2H, d), 3.43 (2H, s), 3.85 - 3.96 (1H, m), 4.44 (2H, s), 6.37 (1H, d), 6.85 (2H, dt), 7.14 (1H, dd), 7.26 - 7.29 (2H, m), 7.37 (1H, d), 7.43 (1H, d)

Example 365

N-(1-benzyl-4-piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

To a solution of 3-(3-Pyridin-2-yl-[1,2,4]oxadiazol-5-yl)-propionic acid (1g) in tetrahydrofuran (5ml), was added carbonyldiimidazole (0.74g). The mixture was stirred for 10 minutes before addition of 1-benzyl-piperidin-4-ylamine (1ml) in tetrahydrofuran (5ml). The reaction mixture was stirred for 15 minutes then partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation. Purification by Biotage® 40S eluting 3%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (0.93g).

MS: ESI 392 (+H)

^{1}H NMR: ($CDCl_3$): δ 1.44 (2H, ddd), 1.88 (2H, d), 2.10 (2H, t), 2.73 - 2.78 (2H, m), 2.80 (2H, t), 3.33 (2H, t), 3.46 (2H, s), 3.75 - 3.86 (1H, m), 5.57 (1H, d), 7.23 - 7.32 (5H, m), 7.42 (1H, ddt), 7.84 (1H, tt), 8.10 (1H, dd), 8.79 (1H, td).

Example 366

N-(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-2-(2-fluoro-phenyl)-acetamide

Step i: (2-Methylamino-ethyl)-carbamic acid tert -butyl ester

To a solution of (2-amino-ethyl)-carbamic acid-*tert*-butyl ester (5g) and triethylamine (6.5ml) in tetrahydrofuran (1000ml) at 0^0C was added methyliodide (1.94ml) dropwise over a period of 1 hour. The mixture was allowed to warm to ambient temperature and stirred for 72 hours before removal of solvents by evaporation. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation to give the title compound (3.7g).

MS: ESI 57($(CH_3)_4C$+), 118 (M+H - $(CH_3)_4C$)

Step ii: (2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester

To a solution of dichlorobenzyl- piperidin-4-one (Example 74, step (i), 4.8g) and acetic acid (1ml) in dichloromethane (100ml) was added (2-methylamino-ethyl)-carbamic acid *tert*-butyl ester (3.26g) and the mixture was stirred for 5 minutes before addition of sodium triacetoxyborohydride (7.9g). The reaction mixture was stirred for 12 hours before addition of sodium bicarbonate solution. The mixture was stirred for ½ hour and then partitioned between water and dichloromethane. The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation. Purification by Biotage® 40S eluting 10%MeOH/2% triethylamine/dichloromethane gave the title compound (1.7g).

MS: ESI 316/318 (+H - $(CH_3)_4COCO$)

^{1}H NMR: ($CDCl_3$): δ 1.44 (9H, s), 1.50 - 1.60 (4H, m), 1.65 - 1.72 (2H, m), 1.95 (2H, td), 2.23 (3H, s), 2.34 (1H, tt), 2.88 (2H, d), 3.14 - 3.20 (2H, m), 3.41 (2H, s), 4.95 - 5.01 (1H, m), 7.13 - 7.15 (1H, m), 7.37 (1H, d), 7.42 (1H, d).

Step iii: N^1-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-N^1-methyl-ethane-1,2-diamine

(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester (1.7g) was dissolved in 6M HCl (20ml) and stirred for 12 hours. The solvent was evaporated and the residue was azeotroped with toluene and then sodium bicarbonate solution was added. The mixture was stirred for 10 minutes and the product was extracted with dichloromethane. The solvent was removed by evaporation to give the title compound (0.75g).

MS: ESI 316/318 (+H)

Step iv: *N*-(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-2-(2-fluoro-phenyl)-acetamide

Prepared by the method of Example 359 step (ii) using N^1-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-N^1-methyl-ethane-1,2-diamine and 2-fluorophenylacetic acid.

MS: ESI 452/454 (+H)

^{1}H NMR: ($CDCl_3$): δ 2.08 – 1.94 (2H, m), 2.37 – 2.33 (2H, m), 2.95 (3H, s), 3.18 (2H, t), 3.41 (2H, m),3.66 – 3.78(4H, m), 3.75 (2H, s), 3.84 (1H, m), 4.38 (2H, s), 7.16 – 7.28 (2H, m), 7.36 – 7.42 (2H, m), 7.45 (1H, dd), 7.73 (1H, d), 7.72 (1H, d).

Example 367

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-*N*-methyl-2-(4-fluorophenyl)acetamide

Step i: [1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-methyl-amine

To a solution of 1-(3,4-Dichloro-benzyl)-piperidin-4-one (3.1g) in dichloromethane (50ml) and acetic acid (0.69ml) was added methylamine (6ml of a 1M solution in tetrahydrofuran). The mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (3g) and the resulting mixture stirred for 72 hours. Sodium bicarbonate solution (100ml) added and the mixture stirred vigorously for 5 minutes before extraction of the product with dichloromethane (2X200ml). The organics were separated, bulked and dried, ($MgSO_4$). Purification by Biotage® 40S eluting 10%MeOH/0.5% 880 ammonia/dichloromethane gave the sub-title compound (1.8g).

MS: ESI 273/275 (+H)

^{1}H NMR: ($CDCl_3$): δ 1.36 (2H, qd), 1.82 - 1.91 (2H, m), 2.03 (2H, td), 2.36 (1H, tt), 2.43 (3H, s), 2.76 - 2.83 (2H, m), 3.43 (2H, s), 7.15 (1H, dd), 7.37 (1H, d), 7.42 (1H, d).

Step ii: *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

To a solution of 4-fluorophenylacetic acid (100mg) in tetrahydrofuran (3ml) was added carbonyldiimidazole (105mg). The mixture was stirred for 10 minutes before addition of [1-(3,4-dichlorobenzyl)-piperidin-4-yl]-methyl-amine (177mg) in tetrahydrofuran (2ml). Stirring was continued for 1 hour then solvent removed by evaporation. Purification by Biotage® 40S eluting 2%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (166mg).

MS: ESI 273/275 (M+H)

^{1}H NMR: ($CDCl_3$) δ 1.57 (1H, d), 1.69 (1H, qd), 1.76 - 1.84 (1H, m), 1.88 (1H, q), 2.10 (2H, td), 2.85 - 2.90 (1H, m), 2.85 (3H, s), 3.42 (2H, s), 3.58 (1H, tt), 3.67 (2H, s), 4.51 (1H, tt), 7.00 (2H, t), 7.11 - 7.15 (1H, m), 7.18 - 7.23 (2H, m), 7.37 (1H, d), 7.41 (1H, dd).

Example 368

N-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyloxy)-acetamide

Step i: Ethyl 2-pyrimidinyloxyacetate

Ethyl glycolate (1.04g) was dissolved in tetrahydrofuran (10ml) and the solution was cooled to 0°C. Sodium hydride (60% suspension in oil, 0.43g) was added and the suspension was stirred and then sonicated in an ultrasonic bath. 2-Chloropyrimidine (1.14g) was added and the mixture was sonicated for a further 110min. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate, the organic phases were washed with brine and dried, filtered and evaporated. The residue was purified by chromatography eluting with *iso*-hexane: ethyl acetate (13:7) to give the subtitle compound (1.40g) as an oil.

^{1}H NMR (299.944 MHz, $CDCl_3$) δ 1.26 (t, J = 6.8 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 4.93 (s, 2H), 6.98 (t, J = 4.8 Hz, 1H), 8.53 (d, J = 4.8 Hz, 2H).

Step ii: 2-Pyrimidinyloxyacetic acid

Ethyl 2-pyrimidinyloxyacetate (1.4g) was dissolved in ethanol (10ml). Sodium hydroxide (2M aq) was added and the mixture was stirred for 64h. The solvent was evaporated and the reside was dissolved in water, filtered and the acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried to give the subtitle compound (0.698g).

^{1}H NMR (399.98 MHz, DMSO) δ 4.85 (s, 2H), 7.09 (t, J = 4.9 Hz, 1H), 8.56 (d, J = 4.8 Hz, 2H).

Step iii: *N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyloxy)-acetamide

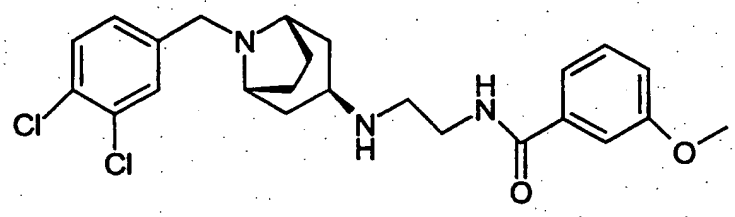
The title compound was prepared from the product of Example 1 step (ii) (hydrochloride salt, 335mg) and 2-pyrimidinyloxyacetic acid (170mg) using the method of Example 94. Yield 140mg.

m.p. 120-122°C

1H NMR (399.978 MHz, $CDCl_3$) δ 1.50 (q, J = 11.6 Hz, 2H), 1.91 (d, J = 11.9 Hz, 2H), 2.13 (t, J = 11.1 Hz, 2H), 2.77 (d, J = 11.4 Hz, 2H), 3.42 (s, 2H), 3.86 - 3.95 (m, 1H), 4.87 (s, 2H), 6.49 (d, J = 6.9 Hz, 1H), 7.05 (t, J = 4.9 Hz, 1H), 7.14 (m, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.42 (s, 1H), 8.57 (d, J=4.8Hz, 2H).

Example 369

N-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt



Step i: 8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one

2,5-Dimethoxytetrahydrofuran (4.92g) was stirred in hydrochloric acid (1M, 25 ml) for 1hour. 3,4-Dichlorobenzylamine (5ml) was added to hydrochloric acid (1M, 15ml) and the resulting suspension was added to the first solution. Phosphate buffer solution (pH 5.5, 250ml) was added followed by sodium hydroxide (1.6g). A solution of acetone dicarboxylic acid (4.77g) in phosphate buffer solution (pH 5.5, 90ml) was added to the mixture and the solution was stirred. A yellow solid formed and the mixture was left to stand for 64h. The aqueous supernatant was decanted and hydrochloric acid (2.5M) was added to the solid along with ethyl acetate. The layers were separated and the aqueous phase was extracted twice with dichloromethane containing a little methanol. The organic layers were combined and evaporated to give a crude oil (ca 7g). A portion of the product (ca 2.5g) was purified by chromatography eluting with dichloromethane : methanol (19:1) to give the subtitle compound (1.62g) as a yellow oil.

^{1}H NMR (299.944 MHz, $CDCl_3$) δ 1.62 - 1.70 (m, 2H), 2.09 - 2.15 (m, 2H), 2.23 (d, J = 15.9 Hz, 2H), 2.67 (d, J = 16.7 Hz, 2H), 3.43 - 3.49 (m, 2H), 3.68 (s, 2H), 7.26 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H)

Step ii: Carbamic acid, Endo-[2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-1,1-dimethylethyl ester

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (751 mg) and carbamic acid, (2-aminoethyl)-1,1-dimethylethyl ester (520 mg) were dissolved in dichloroethane (23ml). Sodium triacetoxyborohydride (697 mg) was added and the suspension was stirred at room temperature for 20hours. Dichloromethane was added and the solution was washed with sodium bicarbonate solution, then with water and then with brine. Chromatography of the residue eluting with ethyl acetate : methanol : triethylamine (80:19:1) gave the subtitle compound (688mg) as an oil.

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.52 (d, J = 14.4 Hz, 2H), 1.96 - 2.09 (m, 6H), 2.67 (t, J = 5.8 Hz, 2H), 2.88 (t, J = 6.4 Hz, 1H), 3.08 - 3.12 (m, 2H), 3.21 (q, J = 5.7 Hz, 2H), 3.48 (s, 2H), 4.80 - 4.95 (m, 1H), 7.22 (dd, J = 8.3, 2.0 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H)

Step iii: *N*-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt

Carbamic acid, [2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-, 1,1-dimethylethyl ester (337mg) was dissolved in dichloromethane (3ml) and trifluoroacetic acid (3ml) was added. The resulting solution was stirred for 1hour then the volatiles were evaporated. The residue was dissolved in dichloromethane (3ml) and triethylamine (1ml) was added followed by 3-methoxybenzoyl chloride (120µl). The solution was stirred overnight. The solvent was evaporated and the residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). Excess tosic acid in ether was added to the residue and the resultant salt was recrystallised from a mixture of ethyl acetate – ethanol with a little cyclohexane to give the title compound (77mg).

m.p. 180-182.5°C

^{1}H NMR (399.98 MHz, DMSO) δ 2.10 - 2.24 (m, 4H), 2.29 (s, 6H), 2.39 - 2.47 (m, 4H), 3.21 - 3.28 (m, 2H), 3.52 - 3.57 (m, 1H), 3.57 - 3.63 (m, 2H), 3.80 (s, 3H), 3.85 - 3.91 (m, 2H), 4.21 (d, J = 5.4 Hz, 2H), 7.11 (d, J = 9.4 Hz, 4H), 7.13 - 7.18 (m, 1H), 7.38 - 7.45 (m,

3H), 7.48 (d, J = 7.9 Hz, 4H), 7.56 (d, J = 6.7 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.84 - 7.90 (m, 1H), 8.38 - 8.52 (m, 2H), 8.81 - 8.87 (m, 1H), 9.44 - 9.51 (m, 1H).

Example 370

Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (350mg) was dissolved in dry methanol (12ml) and ammonium acetate (1g) was added. The mixture was stirred to get partial solution and then sodium cyanoborohydride (106mg) was added. The mixture was heated under reflux for 150 minutes, then allowed to cool to room temperature. The methanol was evaporated, the residue was partitioned between sodium hydroxide and dichloromethane, and the aqueous phase was extracted twice with dichloromethane. The organic phases were combined, dried, filtered and evaporated to give the subtitle compound.

$[M+H]^+$ (ES+) 285

Step ii: Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

3-(2-Pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (305mg) was suspended in dichloromethane (6ml) and oxalyl chloride (0.5ml) was added. The mixture was stirred overnight. Toluene (1ml) was added to the solution, the volatiles were evaporated, then the residue was redissolved in dichloromethane (2ml). Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (all from step(i)) was dissolved in dichloromethane (4ml) containing triethylamine (0.5ml) and then cooled in an ice bath. The acid chloride solution was added to the amine and the mixture was stirred for 1hour. Water was added to the reaction mixture and the phases were separated. The aqueous phase was extracted twice with dichloromethane, the organic phases were dried, filtered and evaporated. The residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). The product was suspended in ether and the ethereal hydrochloric acid was added, the suspension was stirred and then the diethyl ether was evaporated. The residue was dissolved in hot ethyl acetate containing

ethanol and crystallisation was induced by adding *iso*-hexane to give the title compound (47mg).

^{1}H NMR (399.98 MHz, DMSO) δ 1.99 - 1.90 (m, 2H), 2.41 - 2.20 (m, 6H), 2.77 (t, J = 6.8 Hz, 2H), 3.23 (t, J = 6.9 Hz, 2H), 3.81 - 3.72 (m, 3H), 4.15 (d, J = 6.2 Hz, 2H), 7.63 - 7.58 (m, 1H), 7.67 (dd, J = 7.6, 2.3 Hz, 2H), 7.76 (d, J = 9.3 Hz, 1H), 8.06 - 7.99 (m, 3H), 8.11 (d, J = 4.1 Hz, 1H), 8.75 (d, J = 4.6 Hz, 1H), 10.13 (t, J = 5.6 Hz, 1H).

Example 371

2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

Step i: Methyl (4-acetaminophenoxy)acetate

4-Acetaminophenol (1.51g), potassium carbonate (1.38g) and methyl bromoacetate (1.0ml) were combined in acetone (40ml) and heated to reflux for 5hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was dissolved in ethyl acetate, washed with water and then with brine then dried, filtered and evaporated to give the subtitle compound (2.32g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.80 (s, 3H), 4.62 (s, 2H), 6.87 (d, *J* = 9.1 Hz, 2H), 7.07 (br s, 1H), 7.40 (d, *J* = 9.0 Hz, 2H)

Step ii: (4-Acetaminophenoxy)acetic acid

Methyl (4-acetaminophenoxy)acetate was hydrolysed following the method of Example 368 step (ii) to give the subtitle compound (1.85g).

^{1}H NMR (399.98 MHz, DMSO) δ 2.00 (s, 3H), 4.61 (s, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 9.80 (s, 1H).

Step iii: 2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

The title compound was prepared from the product of Example 1 step (ii) (free base, 281mg) and (4-acetaminophenoxy)acetic acid (229mg) using a method hereinbefore described (yield 40mg).

m.p. 177-178.5°C.

^{1}H NMR (299.946 MHz, DMSO) δ 1.51 (qd, J = 10.5, 3.7 Hz, 2H), 1.72 - 1.63 (m, 2H), 2.00 (s, 3H), 2.05 (t, J = 3.7 Hz, 2H), 2.77 - 2.68 (m, 2H), 3.45 (s, 2H), 3.70 - 3.57 (m, 1H), 4.39 (s, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.29 (dd, J = 8.1, 1.7 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 9.79 (s, 1H).

Example 372

N-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-4-hydroxy- benzeneacetamide

The title compound was prepared from the product of Example 1 step (ii) (free base, 172mg) and 4-hydroxyphenylacetic acid (135mg) using a method hereinbefore described (yield 57mg).

m.p. 72-97°C.

^{1}H NMR (399.98 MHz, DMSO) δ 1.37 (q, J = 7.0 Hz, 2H), 1.69 (d, J = 11.3 Hz, 2H), 2.02 (t, J = 5.3 Hz, 2H), 2.71 (d, J = 11.3 Hz, 2H), 3.23 (s, 2H), 3.44 (s, 2H), 3.55 - 3.42 (m, 1H), 6.66 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 9.18 (s, 1H).

Example 373

Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (330mg) was dissolved in tetrahydrofuran (5ml) and cooled to 0°C. Lithium tris (3-ethylpentyl-3-oxy)aluminohydride solution (0.5M, 2.5ml) was added dropwise and the mixture was allowed to attain room temperature overnight. Sodium sulfate decahydrate (ca 2g) was added and the suspension was stirred for 1hour. The reaction mixture was diluted with ethyl acetate, filtered through kieselguhr and evaporated. The residue was purified by chromatography eluting with dichloromethane: methanol (9:1) to give the subtitle compound 161mg.

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.59 (d, *J* = 8.1 Hz, 2H), 1.64 (t, *J* = 11.4 Hz, 2H), 1.86 - 1.81 (m, 2H), 2.00 - 1.97 (m, 2H), 3.21 - 3.18 (m, 2H), 3.55 (s, 2H), 3.95 (septet, *J* = 5.6 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.50 (s, 1H).

Step ii: Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione

Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol (556mg), phthalimide (321mg) and polymer bound triphenylphosphine (821mg) were combined in tetrahydrofuran (10ml). Diethylazodicaboxylate (330μl) was added and the mixture was

stirred gently overnight. Additional phosphine (0.5g) and diethylazodicaboxylate (200µl) were added and the mixture was stirred for an additional 5 days. The reaction mixture was diluted with ethyl acetate and filtered; the residue was washed with ethyl acetate and methanol. The filtrate was evaporated, and chromatographed eluting with 9:1 ethyl acetate : methanol. RPHPLC of the product (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 100% acetonitrile)) gave the subtitle compound (90mg).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.47 - 1.39 (m, 2H), 1.78 (d, J = 7.7 Hz, 2H), 2.14 - 2.02 (m, 2H), 2.64 (t, J = 11.8 Hz, 2H), 3.36 - 3.25 (m, 2H), 3.92 - 3.81 (m, 2H), 4.56 (septet, J = 6.1 Hz, 1H), 7.41 - 7.32 (m, 2H), 7.59 - 7.55 (m, 1H), 7.74 - 7.69 (m, 2H), 7.86 - 7.82 (m, 2H).

Step iii: Exo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (90mg) was dissolved in ethanol (6ml) containing dichloromethane (3ml); hydrazine hydrate (0.2ml) was added and the resulting solution was stirred at room temperature for 26hours. The suspension was filtered and the filtrate was evaporated to give the subtitle compound (55mg).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.51 - 1.43 (m, 2H), 1.59 (q, J = 4.9 Hz, 2H), 1.75 - 1.67 (m, 2H), 2.00 - 1.94 (m, 2H), 3.02 - 2.92 (m, 1H), 3.18 - 3.12 (m, 2H), 3.50 (s, 3H), 7.21 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.50 (s, 1H).

Step iv: Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following the method of Example 370 step (iii) but without salt formation to give the title compound (15mg).

m.p. 177.5-178°C

^{1}H NMR (299.946 MHz, DMSO): δ 1.63 - 1.43 (m, 6H), 1.99 - 1.90 (m, 2H), 2.64 (t, J = 7.1 Hz, 2H), 3.11 - 3.06 (m, 2H), 3.18 (t, J = 6.2 Hz, 2H), 3.49 (s, 2H), 3.97 - 3.83 (m, 1H), 7.32 (dd, J = 8.3, 1.9 Hz, 1H), 7.62 - 7.56 (m, 3H), 7.87 (d, J = 8.1 Hz, 1H), 8.06 - 7.97 (m, 2H), 8.75 (dt, J = 3.7, 0.8 Hz, 1H).

Example 374

(R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinone

(R)-(4-Bromophenyl)ethylamine (1.01g) and potassium carbonate (1.45g) were dissolved in a mixture of ethanol (13ml) and water (6ml) and then heated to a vigorous reflux. A solution of 4-hydroxy-4-methoxy-1,1-dimethyl-piperidinium iodide (J. Chem. Soc. Perkin Trans. 2, (1984) 1647) (1.47g) in warm water (6ml) was added dropwise over 40 minutes; reflux was maintained for a further 12hours, then the reaction was allowed to cool to room temperature. The mixture was evaporated and ethyl acetate and water were added and the phases were separated. The aqueous phase was extracted twice with ethyl acetate, the organic layer was washed with brine, dried, filtered and evaporated. Chromatography of the residue eluting with *iso*-hexane : ethyl acetate (3:2) gave the subtitle compound (804mg).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 2.66 - 2.80 (m, 4H), 1.38 (d, J = 6.9 Hz, 3H), 2.42 (t, J = 6.2 Hz, 4H), 3.58 (q, J = 6.7 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 9.0 Hz, 4H).

Step ii: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinamine

Prepared following the general method of Example 370 step (i) (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinone (420mg) ammonium acetate (0.80g) and sodium cyanoborohydride (120mg) to give the subtitle compound (449mg).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.33 (d, J = 6.9 Hz, 3H), 1.43 - 1.26 (m, 2H), 1.73 (d, J = 12.3 Hz, 1H), 1.81 (d, J = 12.6 Hz, 1H), 2.03 - 1.90 (m, 2H), 2.60 (tt, J = 10.6, 5.1 Hz, 1H), 2.71 (d, J = 13.6 Hz, 1H), 2.94 (d, J = 11.3 Hz, 1H), 3.37 (q, J=6.7 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H)

Step iii: (R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following a method as hereinbefore described using (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinamine (449mg), 3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (0.31g), 1-hydroxybenzotriazole (0.20g), 4-(N,N-dimethylamino)-pyridine (0.13g) and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.30g) to give the title compound (40mg).

m.p. 153-155°C.

^{1}H NMR (399.98 MHz, DMSO) δ 1.23 (d, J = 6.7 Hz, 3H), 1.40 - 1.26 (m, 2H), 1.66 - 1.61 (m, 1H), 1.73 - 1.67 (m, 1H), 1.97 - 1.86 (m, 2H), 2.64 - 2.59 (m, 1H), 2.66 (t, J = 7.2 Hz, 2H), 2.84 - 2.79 (m, 1H), 3.18 (t, J = 7.2 Hz, 2H), 3.42 (q, J = 6.4 Hz, 1H), 3.48 - 3.39 (m,

1H), 7.25 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.59 (ddd, J = 6.7, 4.6, 2.1 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 8.04 - 7.99 (m, 2H), 8.75 (dt, J = 4.4, 1.4 Hz, 1H).

Example 375

(S) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following an analogous series of steps to example 374 but using (S)-(4-bromophenyl)ethylamine to give the title compound.

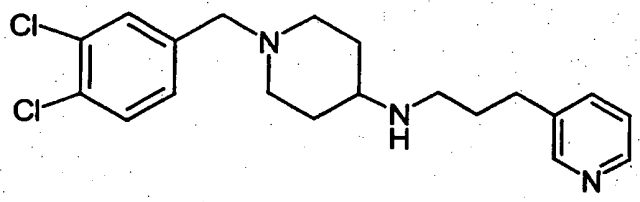
m.p. 141.5-143°C

α_D –29.55° (c= 0.13, methanol, 21°C)

^{1}H NMR (299.946 MHz, DMSO) δ 1.23 (d, J = 6.7 Hz, 3H), 1.26 - 1.41 (m, 2H), 1.64 (t, J = 8.1 Hz, 2H), 1.92 (q, J = 11.2 Hz, 2H), 2.58 - 2.67 (m, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.78 - 2.85 (m, 1H), 3.18 (t, J = 7.1 Hz, 2H), 3.37 - 3.46 (m, 1H), 3.42 (q, J = 6.7 Hz, 1H), 7.25 (d, J = 6.7 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.57 - 7.62 (m, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.98 - 8.05 (m, 2H), 8.75 (d, J = 7.5 Hz, 1H).

Example 385

1-[3,4-Dichlorobenzyl]-N-[3-(3-pyridinyl)propyl]-4-piperidinamine



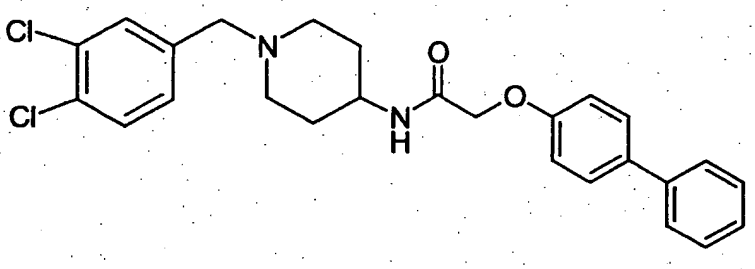
The title compound was prepared from 1-(3,4-dichlorobenzyl)piperidine-4-amine (free base 187mg) , 3-(3-pyridinyl)propanal (125mg), sodium triacetoxyborohydride (70mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane (10ml). Water was added, the mixture neutralised with sodium bicarbonate and the organic phase separated, dried and chromatographed on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (70mg) as a colourless oil.

MS $[M+H]^+$ (ES+) 378

^{1}H NMR: ($CDCl_3$) δ 1.36-1.40 (2H, m), 1.75-1.85 (4H m), 2.0 (2H, t), 2.1-2.2 (2H, m), 2.4-2.45 (1H m), 2.6-2.7 (3H, m), 2.75-2.79 (2H, m), 3.4 (2H, s), 7.1-7.54 (5H, d), 8.44 (2H, m).

Example 386

2-[(1,1'-Biphenyl)-4-yloxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

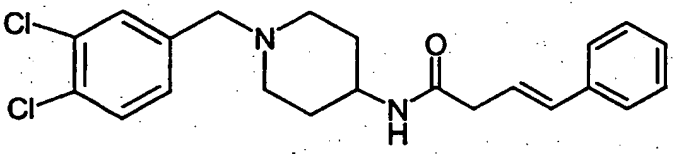


MS $[M+H]^+$ (ES+) 469

^{1}H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.7-1.8 (2H, m), 2.0-2.1 (2H, m), 2.5-2.6 (2H, m), 3.45 (2H, s), 3.65 - 3.7 (1H, m), 4.5 (2H, s), 7.25–7.3 (2H, m), 7.27-7.63 (9H, m), 8.0 (1H, d).

Example 387

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-4-phenyl-3-butenamide

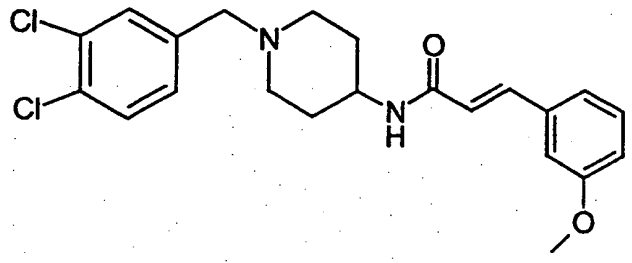


MS $[M+H]^+$ (ES+) 403

^{1}H NMR: ($CDCl_3$) δ 1.46-1.40 (2H, m), 1.85-1.95 (2H, d), 2.05-2.15 (2H, t), 2.75-2.79 (2H, d), 3.1 (2H, d), 3.4 (2H, s), 3.85-3.95 (1H, m), 5.45 (1H, m), 6.3 (1H, m), 6.5 (1H, d), 7.07-7.43 (8H, m).

Example 388

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(3-methoxyphenyl)-2-propenamide.

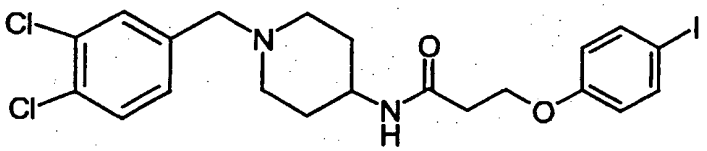


MS $[M+H]^+$ (ES+) 419

^1H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 2.0 (2H, m), 2.15-2.25 (2H, m), 2.75-2.85 (2H, m), 3.4 (2H, s), 3.8 (3H, s), 3.94-4.05 (1H, m), 5.5 (1H, d), 6.35-6.4 (1H, d), 6.9-7.5 (7H, m), 7.6 (1H, d).

Example 389

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(4-iodophenoxy)propanamide.

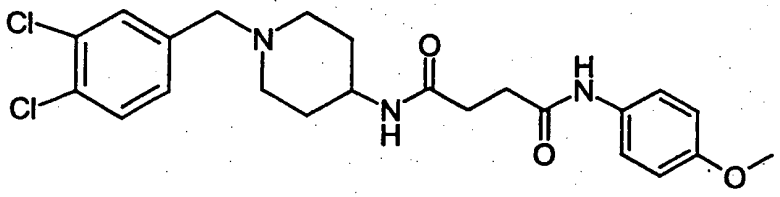


MS $[M+H]^+$ (ES+) 533

^1H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.9 (2H, d), 2.1-2.2 (2H, t), 2.6 (2H, m), 2.75-2.85 (2H, d), 3.4 (2H, d), 3.8-3.9 (1H, m), 4.20 (2H, m), 6.65-6.7 (2H m), 7.1-7.2 (1H, d), 7.35-7.45 (2H, m), 7.54-7.6 (2H, m).

Example 390

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-(4-methoxyphenyl)succinamide

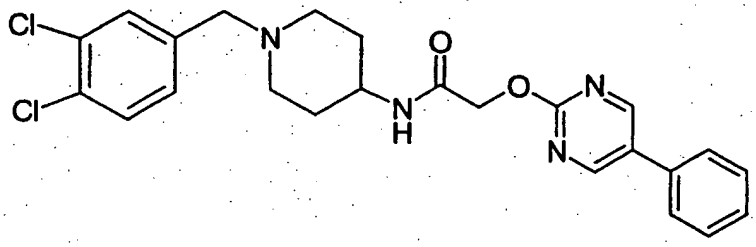


MS $[M+H]^+$ (ES+) 464

^1H NMR: ($CDCl_3$) δ 1.4 (2H, m), 1.6-1.65 (2H, m), 2.05 (2H, m), 2.45 (2H, m), 2.65-2.75 (2H, m), 3.0 (2H, m) 3.45 (2H, s), 3.5 (1H, m), 3.7 (3H, s), 5.9 (1H, m), 6.85 (2H, d), 7.3-7.6 (4H, m), 7.7 (1H, d), 9.7 (1H, s).

Example 391

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)oxy] acetamide

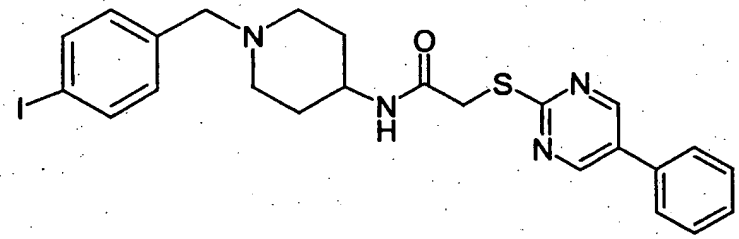


MS $[M+H]^+$ (ES+) 471

^1H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.9-2.0 (2H, m), 2.0-2.1 (2H, m), 2.75-2.85 (2H, m), 3.4 (2H, s), 3.9- 4.0 (1H, m), 4.92 (2H, s), 6.53 (1H, d), 7.1-7.6 (7H, m), 7.7 (1H, s), 8.76 (2H, s).

Example 392

N-[1-(4-iodobenzyl)-4-piperidinyl]-2-(5-phenyl-2-pyrimidinyl)thio]acetamide

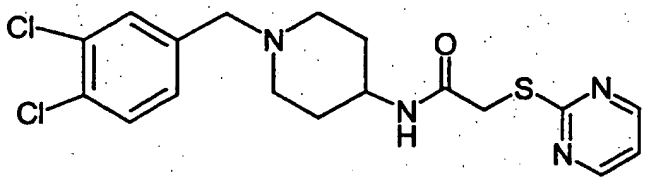


MS $[M+H]^+$ (ES+) 545

^1H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.8 (2H, m), 2.1-2.2 (2H, t), 2.65 (2H, m), 3.4 (2H, s), 3.9(3H, m), 6.8 (1H, d), 7.0 (2H, m), 7.5-7.7 (7H, m), 8.8 (2H, d).

Example 393

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-2-[(2-pyrimidinyl)thio]acetamide

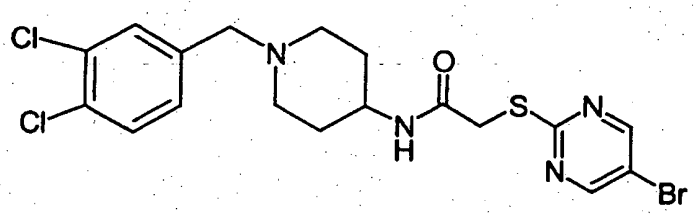


MS $[M+H]^+$ (ES+) 412

^{1}H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.8 (2H, m), 2.1 (2H, m), 2.65 (2H, m), 3.4 (2H, s), 3.8 (3H, m), 6.90 (1H m), 7.05-7.2 (4H, m), 8.58 (2H, d).

Example 394

2-[(5-Bromo-2-pyrimidinyl)thio]-N-[1-(3,4-dichlorobenzy)-4-piperidinyl]acetamide

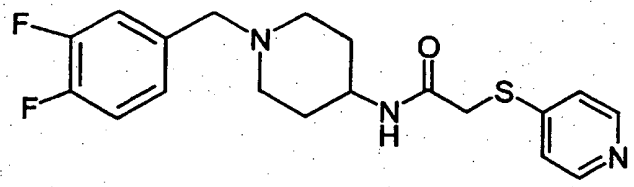


MS $[M+H]^+$ (ES+) 491

^{1}H NMR: ($CDCl_3$) δ 1.46 - 1.50 (2H, m), 1.8 (2H, m), 2.15 (2H, m), 2.6 (2H, m), 3.4 (2H, s), 3.8 (3H, m), 6.6 (1H, d), 7.1 (1H m), 7.3-7.4 (2H, m) 8.58 (2H, d).

Example 395

N-[1-(3,4-difluororobenzyl)-4-piperidinyl]-2-(4-pyridinylthio)acetamide

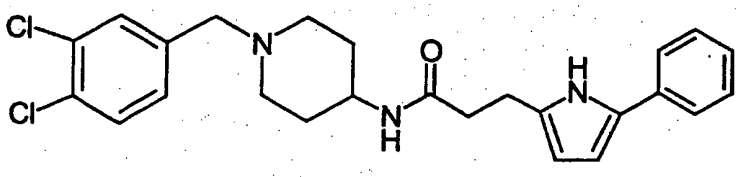


MS $[M+H]^+$ (ES+) 378

^{1}H NMR: ($CDCl_3$) δ 1.36 - 1.40 (2H, m), 1.8 (2H, m), 2.05 (2H m), 2.65 (2H, m), 3.4 (2H.m), 3.67 (2H, s), 3.8 (1H, m), 6.5 (1H, m), 6.9-7.24 (4H, m) 8.48 (2H, d).

Example 396

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-3-(5-phenyl-1H-pyrrol-2-yl)propanamide

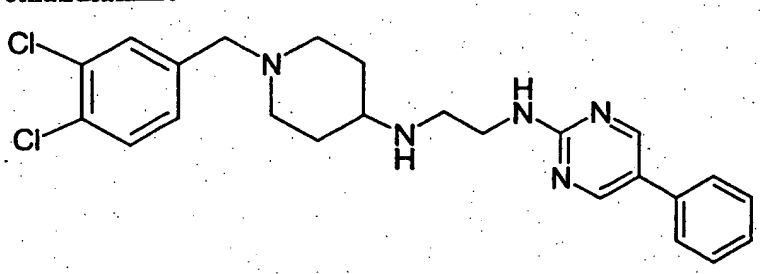


MS $[M+H]^+$ (ES+) 454

^{1}H NMR: ($CDCl_3$) δ 1.36-1.40 (2H, m), 1.87 (2H, m), 2.05 (2H m), 2.5 (2H, m), 2.65 (2H, m), 2.96 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 5.35 (1H, d), 5.95-6.0 (1H, m) 6.38 (1H, m), 7.1-7.5 (8H, m), 9.5 (1H m).

Example 397

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-N'-(5-phenyl-2-pyrimidinyl)-1,2-ethandiamine



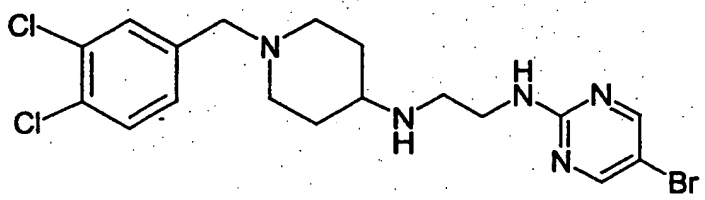
The title compound (20mg) was prepared by heating at reflux N^1-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine (100mg) and 2-chloro-5-phenypyrimidine (100mg) and Hunigs' base (100mg) in toluene for 8hours. The mixture was purified by chromatography on silica, with ethyl acetate methanol (9:1) as eluant to give the title compound as a yellow oil.

MS $[M+H]^+$ (ES+) 456/8

^{1}H NMR: ($CDCl_3$) δ 1.51 (2H, m), 1.75 (2H, m), 2.15 (2H, td), 2.9 (2H, m), 3.05 (1H, m), 3.15 (2H, m), 3.44 (2H, m), 3.8 (2H, m), 6.65 (1H, m), 7.0-7.4 (8H, m), 8.5 (2H, m).

Example 398

N-[5-bromo-2-pyrimidinyl]-N'-[1-(3,4-dichlorobenzy)-4-piperidinyl]- 1,2-ethandiamine



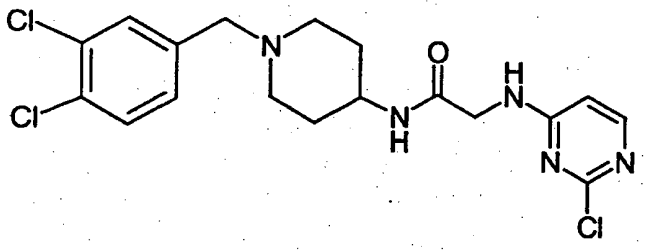
Prepared by the method of Example 397 amine (200mg), 2-chloro-5-bromopyrimidine (130mg), Hunigs' base (200mg) to give the title compound (20mg).

MS $[M+H]^+$ (ES+) 458/60

^{1}H NMR: ($CDCl_3$) δ 1.4 (2H, m), 1.75 (2H, m), 2.05 (2H, td), 2.85 (2H, m), 3.0 (1H, m), 3.15 (2H, m), 3.44 (2H, m), 3.75 (2H, m), 6.8 (1H, m), 7.0-7.4 (3H, m), 8.25 (2H, m).

Example 399

2-[(2-Chloro-4-pyrimidinyl)amino]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl] acetamide

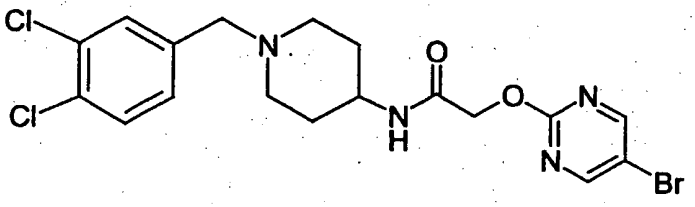


MS $[M+H]^+$ (ES+) 430/32

^{1}H NMR: ($CDCl_3$) δ 1.40 -1.45 (2H, m), 1.97 (2H, m), 2.15 (2H m), 2.75 (2H, d), 3.4 (2H, s), 3.8 (1H, m), 4.05 (2H, d), 5.75 (1H, d), 5.84 (1H m), 6.38 (1H, d), 7.1-7.15 (1H d), 7.36-7.42(2H m), 8.0 (1H d).

Example 401

2-[(5 -Bromo-2-pyrimidinyl)oxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-acetamide

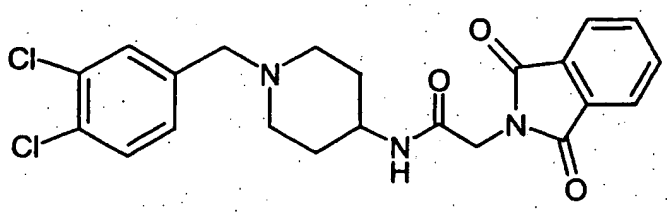


MS $[M+H]^+$ (ES+) 475

^{1}H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.87 (2H, m), 2.15 (2H, m), 2.75 (2H, m), 3.4 (2H, s), 3.9 (1H, m) 4.8 (2H, s), 6.38 (1H, d), 7.1-7.15 (1H m), 7.4 (2H, m), 8.6 (2H, s).

Example 402

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide

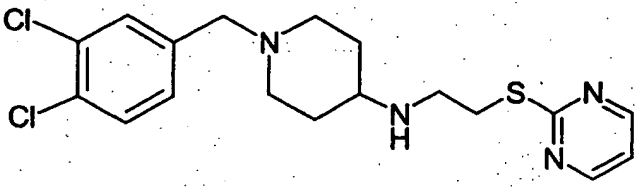


MS $[M+H]^+$ (ES+) 446

^1H NMR: ($CDCl_3$) δ 1.46-1.50 (2H, m), 1.87 (2H, m), 2.15 (2H m), 2.75 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 4.3 (2H s), 5.65 (1H, m), 7.1-7.36 (3H, m) 7.38-7.78 (2H, m), 7.87-7.95 (2H, m).

Example 403

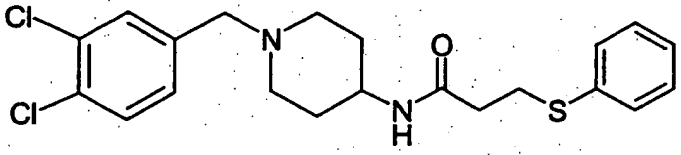
N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[2-(2-pyridinylthio)ethylamine, dihydrochloride



^1H NMR: ($CDCl_3$) (of the free base): δ 1.4 (2H, m) 1.85 (2H, m), 2.05 (2H, m) 2.55 (2H, td), 2.8 (2H, m), 3.0 (1H, m), 3.3 (2H, m), 3.42 (2H, s), 6.9-7.5 (4H, m), 8.5 (2H, m).

Example 404

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(phenylthio)propanamide

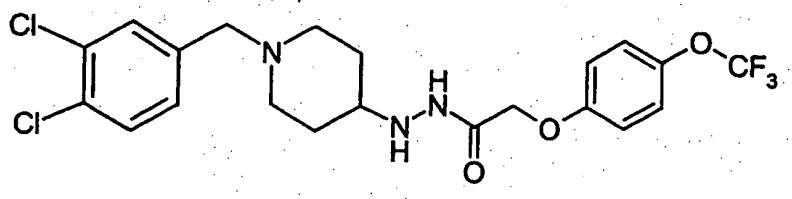


MS $[M+H]^+$ (ES+) 423

^1H NMR: ($CDCl_3$) δ 1.36-1.40 (2H, m), 1.87 (2H, m), 2.15 (2H m), 2.45 (2H, m), 2.76 (2H, m), 3.2 (2H, m), 3.4 (2H, s), 3.8 (1H, m), 5.4 (1H, d), 7.1-7.5 (8H m).

Example 405

N'-[1-(3,4-dichlorobenzyl)- 4-piperidinyl]-2-[4-(trifluoromethoxy)phenoxy] acetohydrazide



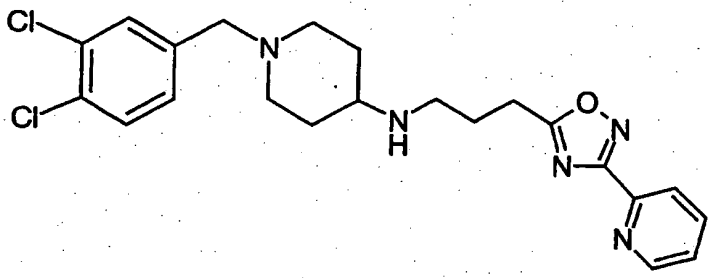
The title compound was prepared from 3,4-dichlorobenzyl-4-piperidone (J. Med. Chem, 1999, 42, 3629; 100mg), 2-[4(trifluoromethoxy)phenoxy]acetohydrazide (100mg), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hours in dichloromethane by the method of Example 369 step ii.

MS $[M+H]^+$ (ES+) 492

^1H NMR: ($CDCl_3$) δ 1.4–1.6 (3H, m) 1.7 (2H, m), 2.0 (2H, m) 2.7-2.9 (2H, m), 3.4 (2H, m), 4.4 (3H, m), 5.3 (1H, s) 6.9 (2H, m), 7.2-7.5 (4H, m), 7.8 (1H, d).

Example 406

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[3-[3-(2-pyridinyl)-1,2,4-oxadiazo-5-yl]propyl]amine



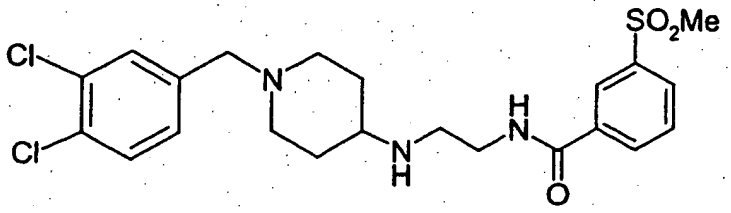
The title compound (29mg) was prepared from 3,4-dichlorobenzylpiperidine-4-amine (100mg free base), 2-[5-(3-bromopropyl)-1,2,4-oxadiazol-3-yl]pyridine (100mg), potassium carbonate (100mg) in dimethyl formamide (1ml) were heated together in the microwave for 30secs,water was added and the product extracted into dichloromethane and chromatographed on silica with ethyl acetate/methanol(9:1) as eluant.

MS $[M+H]^+$ (ES+) 446

^1H NMR: ($CDCl_3$) δ 1.4 (2H, m) 1.7-1.9 (4H, m), 2.0-2.1 (4H, m) 2.46 (1H, m), 2.75 (2H, m), 3.1 (2H, t), 3.4 (2H, s), 7.15-7.45 (4H, m), 7.85(1H, t) 8.1 (1H, d) 8.8 (1H, d).

Example 407

N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-(methylsulphonyl)benzamide



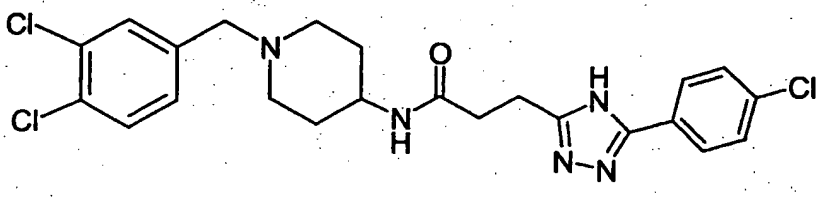
Prepared from *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide (100mg), 3-methylsulphonylbenzoic acid (50mg) and carbonyldiimidazole (40mg). The product obtained was stirred together with sodium hydroxide (40mg) in 50:50 methanol/ water for 12hrs, extracted into dichloromethane and purified by chromatography on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (25mg).

MS $[M+H]^+$ (ES+) 485

^{1}H NMR: ($CDCl_3$) δ 1.4 (2H, m) 1.9 (2H, m), 2.0-2.1 (1H, m) 2.6 (1H, m), 2.8 (2H, m), 2.95 (2H, m) 3.1 (3H, m) 3.4 (2H, s), 3.6 (2H, m), 7.15 (2H, m), 7.4 (2H, m), 7.65(1H, t) 8.1 (2H d) 8.4 (1H, d).

Example 408

3-[5-(4-chlorophenyl-4H-1,2,4-triazol-3-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl])propanamide

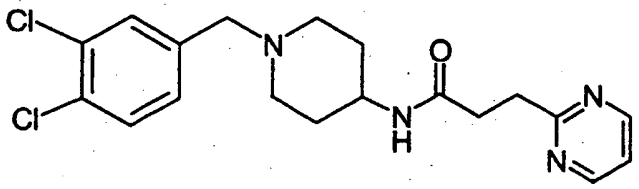


MS $[M+H]^+$ (ES+) 493

^{1}H NMR: ($CDCl_3$) δ 1.6 (2H, m), 1.87 (2H, m), 2.25 (2H m), 2.65 (2H, m), 2.86 (96 (2H, m), 3.14 (2H, m), 3.5 (2H, s), 3.85 (1H, m), 6.0 (1H, m) 7.23 (1H, m), 7.4 (3H m), 7.45 (1H m), 8.0 (2H m).

Example 409

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(2-pyridinyl)propanamide

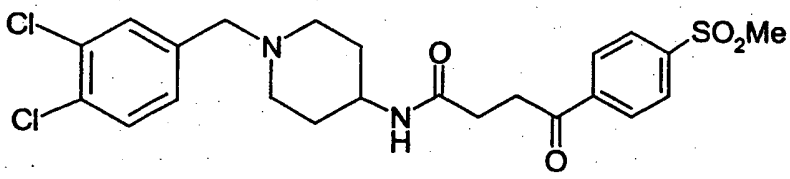


MS $[M+H]^+$ (ES+) 394

^1H NMR: ($CDCl_3$) δ 1.46 (2H, m), 1.8 (2H, m), 2.15 (2H m), 2.75 (4H, m), 3.3 (2H m), 3.45 (2H, s), 3.8 (1H, m), 6.05 (1H, m), 7.1 (2H, m) 7.38 (1H, m), 7.45 (1H m), 8.65 (2H m)

Example 410

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-4-(4-(methylsulphonyl)phenyl-4-oxobutanamide

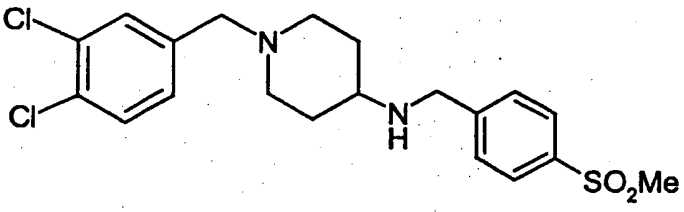


MS $[M+H]^+$ (ES+) 497

^1H NMR: ($CDCl_3$) δ 1.4-1.5 (2H, m), 1.9 (2H, m), 2.15 (2H m), 2.65 (2H, m), 2.78 (2H m), 3.1 (3H s), 3.35 (2H m), 3.4 (2H, s), 3.8 (1H, m), 5.55 (1H, m), 7.16 (1H, m) 7.38 (2H, m), 8.05 (2H m), 8.2 (2H m).

Example 411

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-[4-(methylsulphonyl) benzylamine

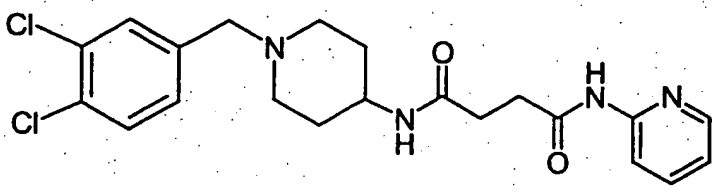


MS $[M+H]^+$ (ES+) 427

^1H NMR: ($CDCl_3$) δ 1.4 (2H, m), 1.8-1.9 (2H, m), 2.0 (2H, m), 2.5 (2H, td), 2.8 (2H, m), 3.0 (2H, s), 3.4 (2H, s), 3.94 (2H, s), 7.15 (1H, m), 7.4 (2H, m), 7.55 (2H, d) 7.9 (2H, d).

Example 412

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-[(2-pyridinyl) succinamide

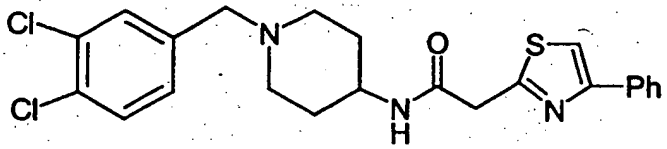


MS $[M+H]^+$ (ES+) 435

^1H NMR: ($CDCl_3$) δ 1.6 (2H, m), 1.87 (2H, m), 2.05 (2H m), 2.65 (2H, m), 2.76 (4H m), 3.4 (2H, s), 3.8 (1H, m), 5.65 (1H, m), 7.0 (1H, m), 7.1 (1H, m), 7.38 (2H, d), 7.7 (1H m), 8.2 (1H m), 8.27 (1H m), 8.65 (1H m).

Example 413

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-phenyl-1,3-thiazol-2-yl))acetamide

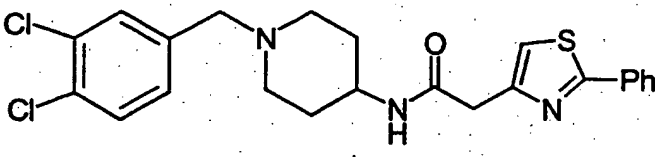


MS $[M+H]^+$ (ES+) 461

^1H NMR: ($CDCl_3$) δ 1.50 (2H, m), 1.87 (2H, m), 2.15 (2H m), 2.65 (2H, m), 3.4 (2H, s), 3.85 (1H m), 4.0 (2H, s), 7.15 (1H, d) 7.3-7.5 (6H, m), 7.9 (2H d).

Example 414

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(2-phenyl-1,3-thiazol-4-yl))acetamide

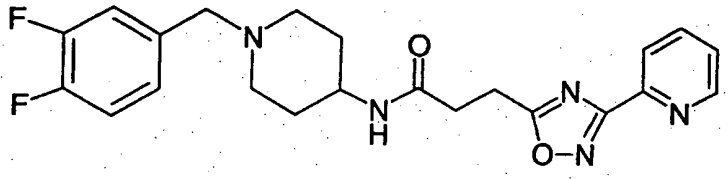


MS $[M+H]^+$ (ES+) 461

^1H NMR: ($CDCl_3$): δ 1.45 (2H, m), 1.90 (2H, m), 2.15 (2H m), 2.65 (2H, m), 3.25 (2H, s), 3.7 (2H, s), 3.85 (1H, m), 7.15 (2H, m) 7.4 (2H, d), 7.5 (3H m), 8.0 (2H m).

Example 415

N-[1-(3,4-difluorobenzyl)-4-piperidinyl]-3-(3-2-pyridinyl-1,2,4-oxadiazol-5-yl]propanamide

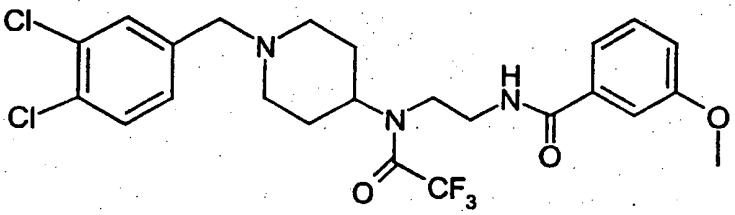


MS $[M+H]^+$ (ES+) 428

^1H NMR: ($CDCl_3$) δ 1.36-1.45 (2H, m), 2.0 (2H, m), 2.1-2.2 (2H, t), 2.7-2.85 (4H, m), 3.34 (2H, d), 3.4(2H, d), 3.8 (1H, m), 5.6 (1H, d), 7.0-7.2 (3H m), 7.4 (1H m), 7.8 (1H, m) 8.1 (1H, d), 8.8 (1H, d)

Example 416

N-trifluoroacetyl-N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-methoxybenzamide



***a) tert*-butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate**

The sub-title compound (800mg) was prepared from 3,4-dichlorobenzyl-4-piperidone (1.3g) *tert*-butyl 2-aminoethylcarbamate (0.8g), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane. The sub-titled compound was isolated by standard procedures.

MS $[M+H]^+$ (ES+) 402

***b) N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide**

A mixture of the above amine (800mg), and triethylamine (0.5ml) in dichloromethane (50ml) , treated with trifluoroacetic anhydride (420mg) over 30 mins, evaporated to dryness and dichloromethane(20ml) and trifluoroacetic acid (2ml) added, stirred for 3hrs, then neutralised with aqueous sodium bicarbonate, the organic phase separated, dried and evaporated to give the title compound (250mg) as a yellow oil.

MS $[M+H]^+$ (ES+) 496/8

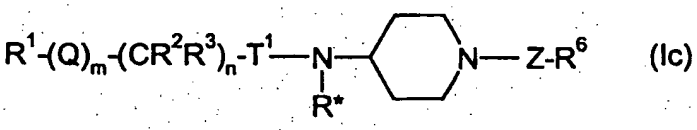
c) N-trifluoroacetyl-N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-methoxybenzamide

The title compound (30mg) was prepared from the product above (40mg) 3-methoxybenzoyl chloride (20mg) and triethylamine (50mg) using one of the methods described above.

MS $[M+H]^+$ (ES+) 580

^{1}H NMR: ($CDCl_3$) δ 0.9 (6H, m) 1.2-1.4 (6H, m), 1.6-1.85 (4H, m) 2.8 (1H, m), 3.3 (4H, m), 3.6-3.8 (5H, m), 3.8 (2H, s), 7.0 (1H, m), 7.1 (1H, m), 7.35-7.45 (3H, m), 8.25(1H, t).

Further compounds of formula (I), all according to formula (Ic), are shown in the table below.



(Ic)

Example	R^1	$(Q)_m$	$(CR^2R^3)_n$	T^1	R*	Z	R^6
380	4-Cl-C_6H_4	O	CH_2	C(O)	H	CH_2C (O)NH	2-Cl-5-CH_3-C_6H_3
381	4-Cl-C_6H_4	O	CH_2	C(O)	H	$(CH_2)_3$	C_6H_5
382	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	O	CH_2	C(O)	H	allyl	C_6H_5
383	2-(cyclopropyl-NH)-pyrimidin-4-yl	m=0	n=0	-	CH_3	CH_2	3,4-Cl_2-C_6H_3
384	2-(pyridin-3-yl)-pyrimidin-4-yl	m=0	n=0	-	CH_3	CH_2	3,4-Cl_2-C_6H_3
400	pyrimidin-2-yl	S	CH_2	C(O)	H	C(O)	3,4-Cl_2-C_6H_3

Pharmacological Analysis

Calcium flux $[Ca^{2+}]_i$ assay

a) Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells

were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

b) Human monocytes

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, J. Leukocyte Biology, 1998, S2, 13). Cells were resuspended ($5x10^6$ ml^{-1}) in LKS and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $0.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Costar). To each well 100μl of cells were added at a concentration of $0.5x10^6$ ml^{-1}. The plates were centrifuged (200g; 5 mins; room temperature) to allow the cells to adhere. After centrifugation the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an A_{50} concentration of MIP-1α and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated $[Ca^{2+}]_i$ in human eosinophils and/or antagonists of the MIP-1α mediated $[Ca^{2+}]_i$ in human monocytes.

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

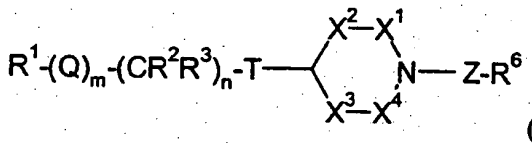
Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% dimethylsulphoxide). The chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

CLAIMS

1. The present invention provides a compound of formula (I):



(I)

wherein

Z is CR^4R^5, C(O) or CR^4R^5-Z^1;

Z^1 is C_{1-4} alkylene, C_{2-4} alkenylene or C(O)NH;

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_{3-7} cycloalkyl, C_1-C_6 alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents C_2-C_6 alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, -NR^7R^8, -$C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl;

wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3-C_7 cycloalkyl optionally substituted by C_1-C_4 alkyl;

T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$;

X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_1-C_4 alkyl or C_3-C_7 cycloalkyl(C_1-C_4 alkyl)} or C=O; or, when they are CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or phenyl(C_1-C_6 alkyl); and,

R^{15} and R^{20} are, independently, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or C_1-C_6 alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_1-C_6 alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is $C(O)NR^{10}$ and R^1 is optionally substituted phenyl then n is not 0.

2. A compound according to claim 1, wherein Q represents a sulphur atom or a group NH, C(O) or NHC(O).

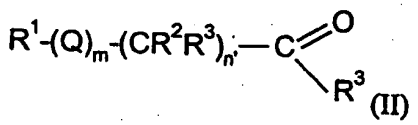
3. A compound according to claim 1 or claim 2, wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. A compound according to any one of claims 1 to 3, wherein X^1, X^2, X^3 and X^4 are all CH_2.

5. A compound as defined in any one of Examples 1 to 416.

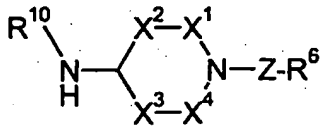
6. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

(a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10}, reacting a compound of general formula



(II)

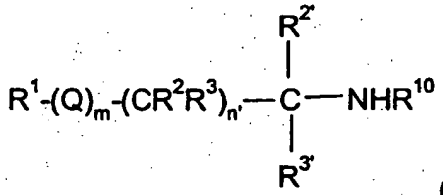
wherein n' is 0 or an integer from 1 to 3 and R^1, R^2, R^3, m and Q are as defined in formula (I), with a compound of general formula



(III)

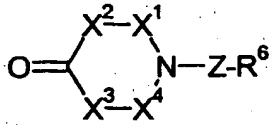
or a salt thereof, wherein X^1, X^2, X^3, X^4, Z, R^6 and R^{10} are as defined in formula (I), in the presence of a reducing agent; or

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1\text{-}C_4 \text{ alkyl})_2$ and T is NR^{10}, reacting a compound of general formula



(IV)

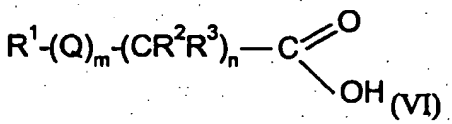
wherein n' is 0 or an integer from 1 to 3, $R^{2'}$ and $R^{3'}$ each independently represent a $C_1\text{-}C_4$ alkyl group, and R^1, R^2, R^3, R^{10}, m and Q are as defined in formula (I), with a compound of general formula



(V)

wherein X^1, X^2, X^3, X^4, Z and R^6 are as defined in formula (I), in the presence of a reducing agent; or

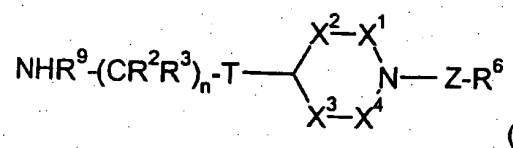
(c) when T is $C(O)NR^{10}$, reacting a compound of general formula



(VI)

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

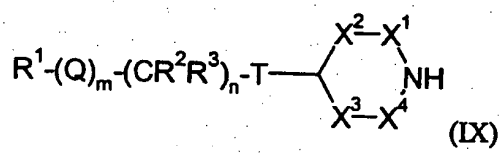
(d) when m is 1 and Q is NR^9, reacting a compound of general formula (VII), R^1 - L^1, wherein L^1 represents a leaving group (e.g. a halogen atom) and R^1 is as defined in formula (I), with a compound of general formula



(VIII)

or a salt thereof, wherein n, T, X^1, X^2, X^3, X^4, Z, R^2, R^3, R^6 and R^9 are as defined in formula (I); or

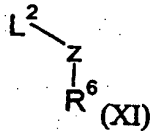
(e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of general formula



(IX)

or a salt thereof, wherein R^1, R^2, R^3, Q, m, n, X^1, X^2, X^3, X^4 and T are as defined in formula (I), with a compound of general formula (X), R^6 - C(O) - R^{20}, wherein R^{20} represents a hydrogen atom or a C_1-C_4 alkyl group and R^6 is as defined in formula (I), in the presence of a reducing agent; or

(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of general formula



(XI)

wherein L^2 represents a leaving group (e.g. a halogen atom) and Z and R^6 are as defined in formula (I); or

(g) when T is NR^{10}, reacting a compound of general formula

$$R^1\text{-}(Q)_m\text{-}(CR^2R^3)_n\text{—}\ L^3 \quad (XII)$$

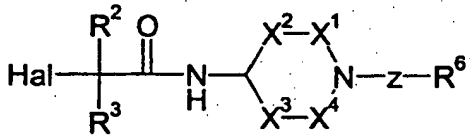
wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1, R^2, R^3, m, n and Q are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when T is $NHC(O)NR^{10}$, reacting a compound of general formula

$$R^1\text{-}(Q)_m\text{-}(CR^2R^3)_n\text{—}\ N{=}C{=}O \quad (XIII)$$

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(i) when T is C(O)NH, Z is CH_2, n is 1, R^2 and R^3 are hydrogen or C_1-C_4 alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV):



(XIV)

wherein Hal is a suitable halogen, R^2, R^3, X^1, X^2, X^3, X^4, Z and R^6 are as defined in formula (I), with R^1OH or R^1SH in the presence of a suitable base;

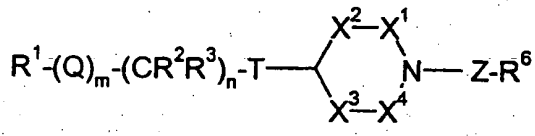
and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 for use in therapy.

10. Use of a compound of formula (I),



(I)

wherein

Z is CR^4R^5, C(O) or CR^4R^5-Z^1;

Z^1 is C_{1-4} alkylene, C_{2-4} alkenylene or C(O)NH;

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_{3-7} cycloalkyl, C_1-C_6 alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents C_2-C_6 alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl); or

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6

alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^7R^8$, $-C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3-C_7 cycloalkyl optionally substituted by C_1-C_4 alkyl;

T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$;

X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_1-C_4 alkyl or C_3-C_7 cycloalkyl(C_1-C_4 alkyl)} or C=O; or, when they are CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1-C_8 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_{1-6} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkylcarbonyloxy(C_1-C_6 alkyl), C_1-C_6 alkyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl$S(O)_2$(C_1-C_6 alkyl), heterocyclyl$S(O)_2$(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)$S(O)_2$, heterocyclyl(C_1-C_6 alkyl)$S(O)_2$, C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, SO_3H, $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1-C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro,

cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or phenyl(C_1-C_6 alkyl); and,

R^{15} and R^{20} are, independently, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_4 alkyl) or C_1-C_6 alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_1-C_6 alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $S(O)_2$(C_1-C_6 alkyl), $C(O)NH_2$, carboxy or C_1-C_6 alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; in the manufacture of a medicament for the modulation of a chemokine receptor.

11. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, as defined claim 10.

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/GB 00/03179

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D401/12 C07D405/12 C07D409/12 C07D417/12
C07D413/12 C07D409/14 C07D413/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 37619 A (OHSHIMA ETSUO ;KYOWA HAKKO KOGYO KK (JP); NAKASATO YOSHISUKE (JP);) 29 July 1999 (1999-07-29) abstract; claims	1-11
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Y	EP 0 903 349 A (HOFFMANN LA ROCHE) 24 March 1999 (1999-03-24) abstract; claims	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2000	05/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 013, no. 072 (C-570), 17 February 1989 (1989-02-17) -& JP 63 264525 A (NIPPON CHEMIPHAR CO LTD), 1 November 1988 (1988-11-01) abstract	1-11
A	WO 97 10207 A (KYORIN SEIYAKU KK ;TAKADOI MASANORI (JP); KOBAYASHI FUMIYOSHI (JP)) 20 March 1997 (1997-03-20) page 18 -page 24 -& DATABASE WPI Week 199719 Derwent Publications Ltd., London, GB; AN 1997-212513 XP002152431 & WO 97 10207 A abstract	1-11
A	WO 97 19060 A (ZENECA LTD) 29 May 1997 (1997-05-29) claims	1-11
A	WO 98 31364 A (HARRISON TIMOTHY ;SWAIN CHRISTOPHER JOHN (GB); MACCOSS MALCOLM (US) 23 July 1998 (1998-07-23) claims	1-11
E	DATABASE WPI Week 200055 Derwent Publications Ltd., London, GB; AN 2000-587420 XP002153516 -& WO 00 53600 A (BANYU PHARMA CO LTD), 14 September 2000 (2000-09-14) the whole document	1-11
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GERARD, CRAIG: "Chemokine receptors and ligand specificity: Understanding the enigma" retrieved from STN Database accession no. 131:198237 CA XP002152430 abstract & CONTEMP. CANCER RES. (1999), 4(CHEMOKINES AND CANCER), 21-31 , 1999,	1-11

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	J HESSELGESSER ET AL: "Identification and Characterisation of Small Molecule Functional Antagonisty of the CCR1 Chemokine Receptor" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 25, 19 June 1998 (1998-06-19), pages 15687-15692, XP002134202 ISSN: 0021-9258 the whole document ---	1-11
A,P	NG H P ET AL: "DISCOVERY OF NOVEL NON-PEPTIDE CCR1 RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY,AMERICAN CHEMICAL SOCIETY. WASHINGTON,US, vol. 42, 4 November 1999 (1999-11-04), pages 4680-4694, XP000887385 ISSN: 0022-2623 the whole document ---	1-11
A	EMONDS-ALT X ET AL: "PHARMACOLOGICAL PROFILE AND CHEMICAL SYNTHESIS OF SR 48968, A NON-PEPTIDE ANTAGONIST OF THE NEUROKININ A (NK2) RECEPTOR" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 3, no. 5, 1993, pages 925-930, XP002068450 ISSN: 0960-894X the whole document -----	1-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.
Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the examples and closely related homologous compounds etc., mentioned in the description wherein Z = CH2; X1,X2,X3,X4 = CH2 and the piperidine possibly bridged; R6 = (opt. subst.) phenyl, benzimidazol-2-yl, indan-2-yl, quinolin-2-yl; R10,R11 = H.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part of the claim(s) may be said to defined a subject-matter for which protection might legitimately be sought (Art. 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently the search has been restricted to the domain ot the claimed activity, i.e. modulators of chemokine receptor activity (description, page 20).
It is noted that claim 5 which makes reference to the description (precisely the examples) is not allowable according to PCT rule 6 (2). As far as the subject-matter of this claim is concerned, the search also cannot be complete.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ial Application No
PCT/GB 00/03179

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			US	6124319 A	26-09-2000
WO 0053600	A	14-09-2000	NONE		